

ajh

AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ARTHRITIS ADVISORY COMMITTEE

Volume I

Tuesday, February 4, 1997

8:15 a.m.

Gaithersburg Hilton
620 Perry Parkway
Grand Ballroom

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666

ajh

Gaithersburg, Maryland

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666

PARTICIPANTS

Michelle A. Petri, M.D., M.P.H., Chairperson
Kathleen Reedy, Executive Secretary

MEMBERS

Steven B. Abramson, M.D.
David T. Felson, M.D., M.P.H.
Felix Fernandez-Madrid, M.D.
Matthew H. Liang, M.D., M.P.H.
Daniel J. Lovell, M.D., M.P.H.
Harvinder S. Luthra, M.D.
Leona M. Malone
Frank Pucino, Jr., Pharm. D.
Lee S. Simon, M.D.
Barbara C. Tilley, Ph.D.

VOTING CONSULTANTS

Joseph McGuire, Jr., M.D.
Andrew Whelton, M.D.

NON-VOTING CONSULTANTS

Karyl S. Barron, M.D.
M. Clinton Miller III, Ph.D.
Patience H. White, M.D.

FDA

Wiley A. Chambers, M.D.
Kent R. Johnson, M.D.

C O N T E N T S

	<u>Page</u>
Introductory Comments: Michelle Petri, M.D., M.P.H.	4
Conflict of Interest Statement: Kathleen Reedy	5
Introductory Comments: Wiley A. Chambers, M.D.	7
Open Public Comments	8
Sponsor Presentation	
Introduction: Michael S. Perry, D.V.M., Ph.D.	9
Clinical Efficacy and Safety: Dosing Guidelines: Helen Torley, M.B., Ch.B., M.R.C.P.	14
Clinical Perspective: Peter Tugwell, M.D.	102
FDA Presentation: Medical: Kent R. Johnson, M.D.	119
Discussion and Questions 1 and 2	144
Pediatric Rule: Lisa Rider, M.D.	223
Sponsor Presentation: Pediatric Data	
Introduction: Michael S. Perry, D.V.M., Ph.D.	225
Summary of Data: Vibeke Strand, M.D., F.A.C.P.	226
Discussion and Question 3	235

P R O C E E D I N G S

Introductory Remarks

DR. PETRI: Good morning. My name is Michelle Petri. I am from Johns Hopkins University. This is the Arthritis Drugs Advisory Committee. I would like to start this morning by asking our panel to introduce themselves. We will start here.

DR. MCGUIRE: I am Joe McGuire, Professor of Dermatology and Pediatrics at Stanford.

DR. WHELTON: Andrew Whelton from the Chicago Medical School, Professor of Medicine and Pharmacology.

DR. FELSON: David Felson from Boston University, Professor of Medicine and Public Health.

DR. TILLEY: Barbara Tilley, Director of Biostatistics and Research Epidemiology at the Henry Ford Health Sciences Center in Detroit.

DR. SIMON: Lee Simon from Harvard Medical School.

DR. ABRAMSON: Steve Abramson, Professor of Medicine from NYU and the Hospital for Joint Diseases.

DR. FERNANDEZ-MADRID: Felix Fernandez-Madrid, Professor of Medicine, Wayne State University.

MS. REEDY: Kathleen Reedy, Executive Secretary of the Arthritis Advisory Committee.

DR. LIANG: Matt Liang. I am an internist and

rheumatologist from Boston.

DR. LUTHRA: I am Harvey Luthra from the Mayo Clinic, a rheumatologist.

MS. MALONE: Leona Malone, Consumer Representative.

DR. PUCINO: Frank Pucino, Department of Pharmacy, National Institutes of Health.

DR. LOVELL: Dan Lovell, pediatric rheumatologist, University of Cincinnati.

DR. MILLER: Clint Miller, biostatistician from the Medical University of South Carolina.

DR. CHAMBERS: Wiley Chambers, Acting Director, Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products.

DR. JOHNSON: Kent Johnson, medical officer, FDA.

Conflict of Interest Statement

MS. REEDY: The conflict of interest statement for the Arthritis Advisory Committee Meeting on February 4, 1997.

The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interest in firms regulated

by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for an appearance of a conflict of interest at this meeting with the following exception.

In accordance with 18 U.S.C. 208(b)(3), a full waiver has been granted to Ms. Leona Malone.

A copy of this waiver statement may be obtained from the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

In addition, we would like to note that Dr. Harvinder Luthra's employer, the Mayo Clinic, has an interest in American Home Products, Lederle, a subsidiary of American Home Products is the manufacturer of a competing product to Neoral, which is unrelated to the firm's competing product.

Although this interest does not constitute a financial interest in the particular matter within the meaning of 18 U.S.C. 208, it could create the appearance of a conflict. However, it has been determined notwithstanding this interest that it is in the Agency's best interest to have Dr. Luthra participate in the committee's discussing concerning Neoral.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are

aware of the need to exclude themselves from such involvements and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firms whose products they may wish to comment upon.

DR. PETRI: Dr. Chambers is now going to give some introductory comments.

Introductory Comments

DR. CHAMBERS: Good morning. On behalf of the Agency, I would like to welcome and thank everyone for their participation. We have designed this particular advisory committee meeting in two parts, one today and one tomorrow, the first part talking about a specific drug, in this case the drug is cyclosporine.

Cyclosporine, as everyone is aware, is a product that is currently marketed, and the application, while it is called a new drug application for administrative purposes, is actually a supplement to the indications or a request for a supplement to the indications where additional indications of rheumatoid arthritis would be added to the currently marketed product.

To that extent, we are clearly interested in both how

the product could be labeled and use, and if the decision is that it should not be labeled for that indication, how we deal with off-label use, because we obviously have to deal with the product that is currently on the market. We do not necessarily expect any controversy in this particular area, but there is no predicting what happens, and we clearly want everybody to speak their minds, so that we can use those opinions.

Tomorrow, the primary purpose is to review a general guidance document. The hope is that this guidance document will serve to assist people in the development of additional products as time goes on.

One of the purposes of scheduling the meeting the way we have is it is sometimes difficult to talk in a complete abstract as far as a guidance document, and we hope that some of the topics that come up today will be useful in the discussion tomorrow.

Thank you.

Open Public Comments

DR. PETRI: We are now going to be opening the open public hearing. We believe that there may be one speaker register, and if we could please start with the Director of Clinical Therapeutics, Dr. Allen Solinger, if he is present today.

[No response.]

Since he does not appear to be present, we would like to have any other organizations or individuals present who wish to make a comment during the open public hearing to go to the center microphone and identify themselves.

[No response.]

Seeing no one, we will now proceed to the sponsor presentation. Before we begin, I would like to request that the different sections of the sponsor presentation be interrupted only if it is necessary for point of immediate clarification. We will have a short period for questions after each of the subsections of the sponsor presentation.

I would now like to introduce Dr. Michael Perry, Vice President, Drug Registration and Regulatory Affairs of Sandoz Pharmaceuticals Corporation.

Dr. Perry.

NDA 50-735, Neoral (cyclosporine) Sandoz

Sponsor Presentation

Introduction

DR. PERRY: Thank you.

[Slide.]

Dr. Petri, Dr. Chambers, Dr. Johnson, Dr. Weintraub, Members of the Advisory Committee, FDA, and guests: Good

morning. I am Mike Perry, Vice President of Drug Regulatory Affairs for Novartis Pharmaceuticals Corporation.

[Slide.]

Please don't let our new name Novartis distract you. Novartis Pharmaceuticals Corporation is the corporate entity which has dawned as the consequence of the merger of Ciba Geigy and Sandoz Pharmaceuticals Corporations.

[Slide.]

Novartis is pleased to have the opportunity to come before you today to present our data on Neoral, our microemulsion formulation cyclosporine. It is important to recognize that two NDAs have been submitted to FDA for the use of Neoral in severe, active rheumatoid arthritis.

[Slide.]

These NDAs represent essentially identical formulations, one for Neoral soft gelatin capsules and a second for the oral solution.

[Slide.]

The specific indication that Novartis is seeking for the use of Neoral is for the treatment of patients with severe, active RA in whom at least one slow-acting second-line drug is ineffective or not tolerated.

Also, we are proposing that Neoral be recommended for use in combination with methotrexate in RA patients who do

not respond adequately to methotrexate alone.

[Slide.]

This slide briefly reviews the general rationale for the use of cyclosporine in rheumatoid arthritis, the active ingredient in Neoral cyclosporine, a product which has been the cornerstone of immunosuppressive therapy in organ transplantation since its original approval in 1983.

This product can be of benefit to RA patients as the chronic joint inflammation which characterizes this disease is recognize to be associated with activated macrophages and T cells, releasing cytokines.

As a well-recognized immunosuppressive agent, cyclosporine is thought to act largely by inhibiting the secretion of such cytokines from T cells, particularly interleukin-2.

[Slide.]

For background purposes, let me take you through a concise regulatory history of cyclosporine. As I mentioned briefly in the last slide, the original formulation of cyclosporine, Sandimmune, has been approved for prophylaxis of organ rejection in the United States since 1983.

In an effort to improve upon the Sandimmune formulation, a microemulsion formulation of cyclosporine, Neoral, was developed and received FDA approval in 1995 for

the same transplantation indications.

There is also extensive experience with cyclosporine in the treatment of rheumatoid arthritis. Globally, to date, more than 20,000 RA patients have been treated with cyclosporine, and specifically with respect to the microemulsion formulation, it is noteworthy to mention that Neoral has been approved for the treatment of severe RA in over 70 countries around the globe.

[Slide.]

Now, the question that I am sure many of you are asking yourselves at this point is specifically how do Neoral and Sandimmune compare with each other. Since most of our clinical studies were conducted with the Sandimmune formulation, it is indeed important that you understand some of the key similarities and differences between the two formulations in order to fully appreciate how the results of the Sandimmune studies apply to the use of cyclosporine in the Neoral formulation.

Firstly, both formulations, Neoral and Sandimmune, share the same active ingredient - cyclosporine. The microemulsion formulation of cyclosporine Neoral was developed in an attempt to overcome some of the imperfections of the Sandimmune formulation, including variable and sometimes poor absorption. Neoral is on

average more bioavailable than Sandimmune. As I stated earlier, some patients absorb Sandimmune poorly, while most patients absorb Neoral well.

In addition, with respect to interpatient variability, exposure to cyclosporine is more consistent from patient to patient with Neoral than it is with Sandimmune.

Finally, and probably most importantly, despite these pharmacokinetic differences between the two formulations, the safety and efficacy of Neoral and Sandimmune in RA are essentially evenly matched.

[Slide.]

In a subsequent presentation, Dr. Helen Torley will be presenting data from our clinical trials. The key points which these data demonstrate are: that Neoral is effective when used in the recommended dose range of 2.5 to 4.0 mg/kg/day; that combination therapy with methotrexate in patients responding inadequately to methotrexate alone provides additional benefit to the RA patient; and that the known and anticipated side effects of cyclosporine treatment, including renal complications, hypertension, and excessive immunosuppression, can be reasonably managed when the oral is used as recommended in our proposed labeling.

[Slide.]

The agenda for the remainder of our presentations is

displayed on this slide. Dr. Helen Torley will be presenting a review of the efficacy and safety data, as well as an overview of our proposed usage guidelines for Neoral in RA.

Following Dr. Torley's presentations, Dr. Peter Tugwell, Chairman of the Department of Medicine at the University of Ottawa, will present a clinical perspective based upon his extensive experience with the use of cyclosporine in rheumatoid arthritis, and as you have seen on the agenda, later in the day there will be a subsequent presentation and discussion regarding the use of Neoral in pediatric RA indications. The presentation for this topic will be given by Dr. Strand, Clinical Faculty at Stanford University.

[Slide.]

Finally, before I turn the podium over to Dr. Torley, I would like to briefly introduce a number of additional experts and consultants who have joined us today for the meeting and discussions.

They include: Dr. Jerry Appel, Director of Clinical Nephrology at Columbia Presbyterian Medical Center; Dr. John Curtis, Professor of Medicine and Surgery and Program Director of the General Clinical Research Center at the University of Alabama at Birmingham; Dr. Marc Hochberg,

Professor of Medicine at the University of Maryland School of Medicine at Baltimore; Dr. Joel Kremer, Head of the Division of Rheumatology at the Albany Medical Center; Dr. Brian Strom, Chair, Department of Biostatistics and Epidemiology at the University of Pennsylvania Medical Center; and Dr. David Yocum, Director of the Arthritis Center at the University of Arizona Health Sciences Center.

I would now like to turn the podium over to Dr. Helen Torley.

Clinical Efficacy and Safety: Dosing Guidelines

[Slide.]

DR. TORLEY: Good morning. My name is Helen Torley and I am the Head of Medical Affairs at Novartis Pharmaceuticals.

[Slide.]

In this overview of the efficacy of cyclosporine in the treatment of rheumatoid arthritis, I will cover the following topics: There will be a description of the study populations involved; a description of the mechanism of action whereby cyclosporine is thought to exhibit its effect; a review of the study designs; a review of the patient characteristics; and the results for Sandimmune and Neoral.

[Slide.]

Now, cyclosporine started being investigated for the treatment of rheumatoid arthritis in the 1980s. The early studies, which are listed on this slide, used initial doses of cyclosporine of over 10 and over 5 mg/kg/day.

While there was evidence of clinical efficacy, it was felt that the renal side effect profile was unacceptable while using these doses.

[Slide.]

More recently, in the late 1980s and early '90s, a series of studies were conducted using a 2.5 mg/kg starting dose, and these are listed on this slide, and include Studies 2008, 651, 652, 653, 302, and 654, and these studies make up the basis of the studies that are considered pivotal and will be proposed to be described in the label for Neoral in the treatment of rheumatoid arthritis.

For completeness sake, you may also hear about the three additional studies, which were one single blind, two open label studies, which started a dose of 3 mg/kg/day, and also two conversion studies, which looked at converting patients stable on Sandimmune therapy to Neoral.

[Slide.]

So the populations that will be presented are summarized in this slide. The labeling studies, as I have described, include the North American placebo-controlled

Studies 302, which compares Neoral with Sandimmune, and Study 654, which compares a combination of Sandimmune and methotrexate in methotrexate inadequate responders versus placebo and methotrexate patients.

There are also descriptions of the CORE studies, which are the North American series of studies, all of which were placebo-controlled, and for the purposes of safety, we have looked at the combined studies, which is all of the studies that I have shown you, and the 3 mg/kg open-label studies, and these are generally presented in the safety section, and won't be discussed in the efficacy section.

[Slide.]

Now, cyclosporine is felt to predominantly work by inhibition of the release of interleukin 2 from the T helper cell. This stops the formation of the T-cytotoxic cells and inhibits the release of interferon-gamma, and indirectly inhibits the release of a number of inflammatory cytokines and other mediators from the macrophages.

[Slide.]

To begin with the study designs, I would like to, first of all, review the designs of the placebo-controlled studies.

Study 651 was a study which compared Sandimmune versus methotrexate and placebo in patients with active rheumatoid

arthritis who had failed at least one slow-acting antirheumatic drug. The study was 24 weeks in duration and involved approximately 284 patients evenly distributed throughout the Sandimmune and methotrexate groups with a 3/3/2 randomization allocating less patients to the placebo group.

Study 652 was conducted to try and determine the lowest effective starting dose of Sandimmune. The study also examined patients with active RA who had failed at least one slow-acting antirheumatic drug. It was 16 weeks in duration, and compared a 1.5 mg/kg starting dose, a 2.5 mg/kg starting dose, and again a placebo group.

The third study, Study 653, was conducted at the request of the FDA. The purpose of this study was not to demonstrate efficacy, but was to determine whether patients could be maintained in a specific target trough level window and find out if this would be a useful way of managing patients in terms of developing clinical response without the adverse safety effects.

The patients were randomized to receive either 1.5, 2.5, or 4.0 mg/kg/day to achieve these target trough level windows. Again, those adjustments were not made on the basis of efficacy, and for this reason the study is not considered a pivotal study for the efficacy of this product.

Study 2008 again looked at patients with active RA, who were previously unresponsive to conventional therapy, and compared 72 patients receiving an initial dose of 2.5 mg/kg of Sandimmune versus placebo.

[Slide.]

Now, moving on to the Neoral versus Sandimmune study, Study 302, this was a 24-week study which had a 28-week double-blind extension. The patients who were involved in the study had severe, active RA in whom treatment with slow acting antirheumatic drugs was either ineffective or inappropriate.

It involved 144 patients being randomized to the Neoral 2.5 mg/kg starting dose, and 155 randomized to the Sandimmune 2.5 mg/kg starting dose.

[Slide.]

Finally, in terms of this series of study designs, the final one is Study 654, which examined the combination of Sandimmune plus methotrexate versus placebo plus methotrexate in patients determined by their physicians to be experiencing an inadequate response to methotrexate.

To be eligible for entry, the patients had to be receiving doses of methotrexate less than or equal to 15 mg/week, and on top of this, Sandimmune at a starting dose of 2.5 mg/kg/day or placebo was added.

There were 75 patients randomized to the Sandimmune/methotrexate group, and 73 to the methotrexate plus placebo group.

[Slide.]

In terms of patient demographics, first of all, looking at the placebo-controlled studies, we can see that the mean age across all studies was around the age of 50, and as expected, the predominance was of females entered into these studies.

RA disease duration across the studies was generally in excess of 10 years, and the large majority of patients in each study was also receiving concomitant nonsteroidals and concomitant steroids.

Concomitant steroids were permitted in the study provided the dose was less than 10 mg/day and that every attempt was made to maintain the dose at that throughout the duration of the study. Patients were asked to be on a stable dose of nonsteroidals prior to entry into the study and again for every attempt to be made to keep the dose stable throughout the duration of the study, and not change nonsteroidals.

[Slide.]

Study 302 really shows a very similar picture. Again, predominantly females in the mid-50s age range with a

disease duration in excess of 10 years. In the study, we have information on the number of slow-acting antirheumatic drugs failed prior to entry into the study and mean in both groups was 3.4 failures.

Again, concomitant NSAIDS and steroids were used in the majority of patients. In this study and indeed in 2008 and 652, over 70 percent of the patients who entered these studies had actually failed methotrexate therapy.

[Slide.]

Finally, Study 654, a very similar picture not to belabor the point. Females 50s, mean number of second-line drugs failed prior to entry into the study was 2.4. Mean disease duration around the 10-year mark, and again concomitant NSAIDS and steroids in the majority of patients.

[Slide.]

In terms of disease activity on entry into the study, the study protocol stated the patients had to have a history of active RA affecting more than 20 joints and have more than 6 active joints on study entry in terms of painful or swollen.

This slide represents the baseline swollen joint count by study and tender joint count by study. You can see that on average, the swollen joint counts, the patients ranged from about 15 to 20 as a range of the mean across the study

and tender joint count was a little bit higher across the study, indicating patients did indeed have active joint disease on entry into the study.

[Slide.]

Now, this was the dose titrations. So far we have only discuss the starting dose of Sandimmune and Neoral in the studies, which was every study I have presented included an arm that started at 2.5 mg/kg/day.

In Study 2008, the dose titration instructions were initially given that the goal was to reach the target trough level which was defined at that time. However, because blood levels were found to be too inconsistent, actual dose adjustments were made to increase the dosage until the serum creatinine rose.

In Study 651 and 652, the dose was held stable for eight weeks at 2.5 and then had to be increased in increments of 50 or 100 mg, and the dose was not allowed to exceed a total of 5 mg/kg/day.

In Study 302, dose increases were permitted after four weeks in this study, and the dosages were selected. After 2.5, the patient could be increased to 3.3, 4.2, then, 5 mg/kg/day, and again, 5 mg/kg/day was the maximum dose that was to be permitted.

In Study 654 finally, this study recommended increasing

the does by 0.5 mg/kg at weeks 2 and 4 if the serum creatinine permitted that, and then at weeks 8 and 16 if there was a lack of clinical response. Again, the maximum dose to be permitted in the studies was 5 mg/kg/day.

[Slide.]

Now, this slide summarizes before we get into the efficacy presentation of the results, the range of doses that the patients actually received in the studies and the mean dose in the patients who remained in the study at final visit.

As we can see from each of the studies, there is a wide range of doses from below 1 mg/kg/day to just about 5 in the majority of studies with Study 302 sticking out with one patient here receiving a dose of 9.26 mg/kg/day. The mean dose at the final study visit is anything from approximately 3 mg/kg/day when cyclosporine was used a monotherapy and 2.8 mg/kg/day when it was used in combination.

[Slide.]

Looking at how many patients completed these studies, just to remind you, Study 651 and 2008 were both 24 weeks in duration, and we can see that in Study 2008, 86 percent of patients completed the study in the Sandimmune group versus 57 percent in the Study 651, again, the range was between these two for patient completions.

The primary cause for discontinuation in most of the studies was adverse reactions as a result of cyclosporine therapy, the one difference being Study 651 where more patients discontinued for lack of efficacy.

[Slide.]

A similar picture was seen in Studies 302 and 654 where 68 percent of Neoral and 63 percent of Sandimmune patients completed 24 weeks, and in the combination study, 76 percent of Sandimmune/methotrexate completed 24 weeks versus 84 percent in placebo. Again, causes for discontinuation were predominantly due to adverse events with lack of efficacy being a very uncommon reason for discontinuation.

[Slide.]

Now, I would like to move into a presentation of the efficacy results. First of all, I will present to you the primary efficacy variables as they were stated in the individual protocols. At the request of the FDA, we have also done an analysis looking at the ACR Responder Index, which is only looking at patients who complete the studies who can be considered to be responders.

[Slide.]

Starting, first of all, with Study 651, if we concentrate first on the 2.5 mg/kg/day group of Sandimmune, we can see that compared to placebo, there was a

statistically significant improvement in swollen joint count and in patient global, MD global, and in the health assessment questionnaire.

The methotrexate group showed a considerably greater response than the Sandimmune group and again it was statistically superior to both Sandimmune and placebo in this study.

[Slide.]

Study 652, first of all, looking at the 1.5 mg/kg/day arm, we can see that in none of the parameters here at end point was a statistical difference seen when compared to placebo. The 2.5 mg/kg/day starting dose group, however, did show a significant improvement in all of the primary efficacy group criterias that were stated in the protocol.

[Slide.]

Study 653, shown here very briefly just for completeness sake shows that the patients and MD globals showed statistical improvement versus placebo for the 2.5 and 4.0 mg/kg/day group, but as previously stated, because the primary goal of this study was not to titrate for efficacy, these results will not be further discussed.

[Slide.]

Study 2008, the Sandimmune versus placebo study, again a statistically significant improvement versus placebo were

seen for all of the primary efficacy variables at study end point.

[Slide.]

In Study 302, which compares Neoral versus Sandimmune, we can see that there was very similar efficacy between the two treatment arms, Sandimmune and Neoral, and the range of efficacy seen in these studies is very similar to those results I just showed you for the placebo-controlled studies. In only one variable was Neoral superior to Sandimmune, and that was the patient global at the 24-week end point.

[Slide.]

Finally, Study 654, again the arm which had the Sandimmune plus methotrexate inadequate responders was statistically superior to the group maintained on their entry dose of methotrexate to which placebo was added with statistically significant difference being present in all of the primary efficacy variables at study end point.

[Slide.]

Now, I would like to describe to you the result of the ACR Responder Index. Because a number of these studies were conducted prior to the publication of the ACR Responder Index we do not have all of the required efficacy variables captured.

For Studies 651 and 652, visual analogue scale pain was not captured, and for a patient to be considered a responder in these two studies, the patient had to complete the study and have an improvement in swollen and tender joint count and in two of the four of the remaining variables for which we had data captured.

Similarly for Study 2008, the health assessment questionnaire was not captured on all patients. Here, again a patient was considered a responder if they complete the study and had a 20 percent improvement in swollen joint count, tender joint count in two of four remaining variables.

Studies 302 and 654, which were conducted more recently, do have all of the variables collected.

[Slide.]

Beginning, first of all, with the placebo-controlled studies, this slide represents the percentage of patients achieving the ACR Responder Index by dosage group, and if we look at, first of all, Study 651, we can see that in the Sandimmune group, 25 percent of patients achieved the ACR Responder Index by the definition versus 39 percent in the placebo group. The difference between the Sandimmune group and the placebo group in terms of responders was statistically significant. I would remind you that the mean

dose at the end point of the study was 3.1 mg/kg/day for this study.

In Study 652, starting first of all with the 1.5 mg/kg group, we can see that the 19 percent responder rate in this group versus the 16 percent in the placebo group did not achieve statistical significance, again indicating this is not an effective starting dose.

If we look at the 2.5 mg/kg/day group, we can see that 33 percent of patients achieved the ACR Responder Index, which was statistically significant versus placebo. In this group of patients, the mean dose at last visit was 2.9 mg/kg/day.

Study 2008, again a 35 percent responder rate in the Sandimmune group versus 7 percent in placebo, statistically significant and the mean dose was 3.6 mg/kg/day.

[Slide.]

Moving on now to Studies 302 and 654, the Neoral arm shown in green here, showed a 30 percent responder rate at week 24 versus 23 percent in the Sandimmune group, very much in line with the results I just showed you for the placebo-controlled studies.

In Study 654, we see with the combination arm, Sandimmune and methotrexate, a 43 percent responder rate versus 14 in the placebo group. Again, this was

statistically significant and the dose in the end point here was 2.8 mg/kg/day.

[Slide.]

Now, how long does it take for cyclosporine to begin to work? This slide looks at the time to onset of response by the percent responders over time. Looking at the Studies 651, 652, and 2008, we can see a divergence between the Sandimmune groups and the placebo groups occurring as early as week 4 with statistically significant differences between the two occurring at week 8.

[Slide.]

Similar results seen in 654, the combination study. Here, we see the divergence in efficacy at around about week 8, at which time the responder rate in the combination arm was statistically significant when compared to the responder rate in the placebo arm indicating that the onset of efficacy occurs between weeks 4 and 8 and increases with time.

[Slide.]

Now, we have taken a look at the long-term effect of cyclosporine. The data I have shown you so far only goes out to week 24. In Studies 651 and 652, there were long-term extensions which are open to these studies, and we present this data purely for descriptive reasons.

This slide illustrates the change in swollen joint count from baseline in Study 651. This study did have a dose taper and washout period, so this is why there is this break in the data here with patients who received Sandimmune in the original study being complemented with patients who received methotrexate and placebo, Neoral receiving cyclosporine in the extension phase.

As we can see, the maintenance of effect as determined by the change in swollen joint count was maintained over a duration of up to 104 weeks.

[Slide.]

Similarly, in Study 652, here again we had a period of washout and then patients who were on placebo were allowed to enter the extension study. We see in the double-blind portion there is a reduction in mean swollen joint count. This is also seen in the patients who entered the extension with the effects maintained out to 104 weeks.

[Slide.]

Looking at Study 654, this slide represents the change in swollen joint count that occurred during the combination study, and this follows a cohort of 113 patients who potentially could have been eligible for receiving a full two-year course of therapy.

We can see that the patient numbers do dwindle towards

the end, but again over the course of period, the effect is maintained in terms of reduction of swollen joint count.

Similarly, just looking at the ACR Responder Index at week 24, 52 percent of patients on the combination arm were responders and at week 48, the number was 50 percent. This represents the ITT population, not the completer population I presented previously, and that is the reason for the slight difference in the numbers here.

[Slide.]

Now, does cyclosporine work once the drug is withdrawn? Studies 651 and 652 had dose taper and washout periods. Study 651, a four-week taper and a four-week washout study; Study 652, a one-week taper and a four-week washout.

This column here represents the mean change from baseline tender joint count the final week of treatment and what happened to that tender joint count in those patients at the end of washout.

We can see that between the five to eight-week washout period, the majority of the benefits of cyclosporine are lost, indicating that cyclosporine's effects are only going to be present while the drug is being administered.

[Slide.]

So, in summary, then, cyclosporine Neoral and Sandimmune produces a statistically and significant

improvement in the signs, symptom, and function of RA disease activity.

Neoral seemed to produce comparable efficacy to Sandimmune and the onset of action occurs between four and eight weeks. An initial dosage of 2.5 mg/kg/day titrated for clinical response and safety is recommended, and the addition of cyclosporine Neoral and Sandimmune to the treatment of patients responding inadequately to methotrexate alone would seem to confer a statistically significant clinical benefit.

Thank you.

DR. PETRI: I would like to open this up for a brief discussion at this point. Dr. Torley, if you could actually stay at the microphone for us.

Are there questions from the panel about this part of the presentation? Dr. Abramson.

DR. ABRAMSON: I just was curious. In any of the studies were people treated with cyclosporine after having failed only one slow-acting drug? I saw this data on two and three.

DR. TORLEY: There were patients who entered the study who only failed one. I would say given the disease duration we saw of a mean of 10, the majority of patients had failed probably more than one, but we do have a few patients who

had only failed one slow-acting antirheumatic drug.

DR. PETRI: Dr. Torley, you may want to defer this question to Dr. Tugwell, do you have data to show us on drug interactions specifically with calcium channel blockers and with grapefruit juice from your studies?

DR. TORLEY: We certainly can address that in the question section. In our clinical studies, we prohibited the use of the calcium channel blockers, interfere with cyclosporine. The grapefruit juice is a more recent event that we didn't prohibit in our studies, so we cannot comment on that. But drugs that we knew that inhibited or potentiated cyclosporine's blood levels or drugs that we needed added to the neurotoxicity were prohibits from our studies.

DR. FERNANDEZ-MADRID: However, the compliance problem was indicated in some of the studies, I think in 25 percent in one of the studies, some prohibited drugs were used, and perhaps some of these were the sort, calcium channel blockers or some others.

Do we know which drugs were used that were prohibited?

DR. TORLEY: I would say from my memory, the most commonly used prohibited drug were the H2 antagonists. They are frequently used in RA patients, and we did prohibit them from our study because of a potential interaction. I would

say that is the commonest class of drugs used.

DR. PETRI: Dr. Lovell.

DR. LOVELL: I have a question about your time to response, and I ask this in reference to the labeling that says if a patient has not responded by 16 weeks, then, you should discontinue the drug, but it looks like from your slide and a review of the data that almost half of your responders did so after 16 weeks. So, I would like to see what you thought about that particular wording in the labeling.

DR. TORLEY: Right. I believe that that was added more to try and be in line with an analysis that had been done that if you hadn't responded or shown any response by 16 weeks, you were less likely to have a response.

I agree there are patients who do respond after 16 weeks to some degree.

DR. LOVELL: I think it is almost half of the patients who eventually show response a response and in this drug whose use is going to be patients who have failed many other standard therapies, I think perhaps it would be more proper to indicate that a large number could potentially still respond after that 16-week mark, because the alternatives for these patients are really quite small by the time they get to the point where they are going to use cyclosporine

given the indications in the labels.

DR. TORLEY: I would actually agree with that, yes.

DR. PETRI: Dr. Tilley.

DR. TILLEY: I had two questions. First, how did you define complete for your ACR criteria? You said patients had to be complete the study. What was your definition of complete?

DR. TORLEY: The patient had to fulfill all of the assessments that were dictated by protocol at the final study visit, which was different for each study. For Studies 654 and 2008, they had to get to week 24 and complete that visit. For Study 652, it was a week 16 visit. It was a protocol-stated end point of the studies.

DR. TILLEY: Did it have anything to do with whether they were on medication or not on medication, or was it just that they had the follow-up assessment?

DR. TORLEY: They were all on study medication.

DR. TILLEY: So, they had to be on medication.

DR. TORLEY: They had to be on medication.

DR. TILLEY: And complete the --

DR. TORLEY: Yes, right.

DR. TILLEY: Did you do any formal tests of the equivalent statistical tests of equivalence for the SIM versus Neoral?

DR. TORLEY: I think I will defer that one to one of my statistical colleagues. Dr. Lin?

DR. TILLEY: We can wait for that for later, if you would like.

DR. TORLEY: Okay.

DR. PETRI: Dr. Lin, would you like to address that now?

DR. LIN: Would you please repeat the question?

DR. TILLEY: I was just wondering if you had done any formal statistical tests with respect to the equivalence of Neoral and SIM rather than just making those two comparisons and saying that there was no statistically significant difference. Did you do any statistical testing that would be looking at the question of equivalence?

DR. LIN: The answer is negative, no, we did not.

DR. TILLEY: Thank you.

DR. PETRI: I don't see any further questions from the panel, so we welcome having Dr. Tugwell's presentation now. Thank you, Dr. Torley.

DR. TORLEY: Actually, the safety presentation is next.

DR. PETRI: Thank you.

[Slide.]

DR. TORLEY: This slide summarizes the patient populations that I have described to you already who were

involved in the clinical study program by the duration of cyclosporine exposure.

We can see in terms of number of patients who were exposed for period of greater than 12 months. The total number is 600 patients. Eighteen months was 276, and 24 months the total number of patients exposed over this period of time was 134.

[Slide.]

In your briefing books there are extensive lists of the adverse event rates that were reported both in Sandimmune versus placebo group, the methotrexate combination arm versus the methotrexate alone group, and the Neoral versus Sandimmune group.

In the interests of brevity in this presentation, I won't go into that in detail, but we will be pleased to answer any questions you have following this presentation.

I would like to summarize what the key findings in those adverse event comparisons were. The adverse events which were seen to occur more frequently with Sandimmune than with placebo, were in the GI system, nausea and dyspepsia; in the central nervous system, headache, dizziness, and paresthesia; in the cardiovascular system, hypertension and chest pain; in the skin system, hypertrichosis; and in the renal system, serum creatinine

increase.

In the combination arm where Sandimmune and methotrexate were added together, it resulted in a very similar adverse event profile to the methotrexate-alone arm, however, hypertrichosis and serum creatinine were seen more commonly with Sandimmune a methotrexate, and there were more upper respiratory tract infections in the combination arm. However, this did not reach statistically significance.

Neoral was found to have a similar adverse event profile to Sandimmune.

[Slide.]

In terms of the adverse events that resulted in dropouts for patients, this summarizes the results from the CORE North American studies - Study 651, 652, 653, and 2008.

First of all, looking at the Sandimmune arm, you can see the two commonest causes for discontinuation in 4 percent of patients were the GI system, this was predominantly nausea and vomiting, and in the laboratory system arm, it was predominantly serum creatinine increases.

There were also some discontinuations in the placebo group for GI events, and that was the most common cause for discontinuation in the methotrexate arm.

All other reasons for discontinuation in the cyclosporine arm occurred with the frequency of less than or

1 percent.

[Slide.]

Now, looking at the number of deaths that have been reported to Novartis either during or following clinical study participation, this was the number that we have been reported is 19 in the Sandimmune arm and one patients in the Neoral arms.

The causes for death are listed on this column. The two commonest causes were neoplasia in five patients and cerebral vascular reasons in four patients. Two of these were myocardial infarctions and one was a sudden death, and I believe the other one was a myocardial infarction, too.

[Slide.]

If we actually compare the rates of death in the placebo-controlled studies, which do allow an accurate comparison given that the duration of follow-up in this group is extremely long, we can see that in the placebo-controlled studies, there were three deaths in the Sandimmune group, which were caused by brain carcinoma, pancreatitis and sepsis, which compares with an overall rate of two in the placebo-controlled arms from cytogenic purpura and pulmonary embolism.

[Slide.]

Now, as you have heard, cyclosporine has been used

since 1983, and over 100,000 total transplant patients have received cyclosporine, and its safety profile has been fairly well characterized in that population.

In RA patients, I would like to focus on three special safety concerns and to discuss these in depth with you what the findings, and also our recommendations for management of these particular issues.

[Slide.]

First of all, beginning with the cyclosporine renal effects. Cyclosporine has two effects in the kidney. Firstly, a functional change can occur, and secondly, morphological alterations have also been seen.

[Slide.]

Beginning, first of all, with the functional changes, these are the result of vasoconstriction of the glomerular afferent arteriole, which leads to reduction in renal blood flow, a reduction in GFR, and a resultant increase in serum creatinine levels.

[Slide.]

Cyclosporine associated nephropathy is characterized by tubulointerstitial changes and arteriolar alterations, and classically presents as a focal interstitial fibrosis, which may be striped, and the presence of tubular atrophy.

In terms of the arteriolar alterations, classically, we

get a cyclosporine arteriopathy and presence of intimal hyalinosis.

[Slide.]

Now, the largest series of biopsies we have in autoimmune disease patients who have received cyclosporine in which a risk factor assessment was done was a series of 192 patients with immune-mediated diseases. These were predominantly patients with juvenile diabetes, polychondritis, and psoriasis, who were treated with doses of cyclosporine ranging from 3 to 10 mg/kg/day, which is, as you will note, much higher than we currently recommend, and for treatment duration periods of 4 to 39 months.

In this group, a risk factor assessment was done on the patients who did develop nephropathy, and the following factors were found to be significantly associated with that risk.

These include the maximum serum creatinine increase, the maximum Sandimmune dosage, and the age of the patients. It is of note that these factors listed here were not found to have a significant association and include the duration of Sandimmune treatment, the duration of serum creatinine increase, and hypertension. On the next two slides, these data are illustrated.

[Slide.]

This first slide shows the maximum serum creatinine increase above baseline on this axis, and the incidence of morphological moderate or severe alterations characteristic of cyclosporine nephropathy.

We can see that in the two groups in whom the maximum creatinine increases kept to less than 50 percent above baseline, these are the patients who have the lowest incident of developing cyclosporine nephropathy. As a maximum increase of serum creatinine is allowed to increase, so, too, does the incidence of cyclosporine nephropathy. This is data that gave rise to the dosing guidelines of always keeping the serum creatinine to below 30 percent.

[Slide.]

Similarly, for dose, again, the same type of slide with the maximum cyclosporine does shown on this axis, and the incidence of moderate or severe cyclosporine nephropathy on this axis. We can see that in the patients whose dose was kept below 5 mg/kg/day, none of these patients developed evidence of cyclosporine nephropathy, but as the dose was allowed to increase, so, too, did the incidence of nephropathy. Again, it was this data that gave rise to the guideline that the dose of cyclosporine should always be kept below 5 mg/kg/day.

[Slide.]

Now we have more limited biopsy data in rheumatoid arthritis population, and this slide represents a plot of the maximum Sandimmune dosage versus the maximum serum creatinine increase in a total of 60 patients with rheumatoid arthritis who underwent renal biopsy, the majority of whom did so for protocol reasons, and not for renal toxicity reasons.

Shown in the white squares are the patients who had no evidence of cyclosporine nephropathy, and shown in the orange squares are the patients with cyclosporine nephropathy. We can see that according to the dosing guidelines I have just mentioned, keeping the maximum Sandimmune dosage less than 5, and the maximum serum creatinine increase below 50 percent or indeed below 30 percent, only one of the patients who had an abnormal biopsy fell into this category.

[Slide.]

This one patient that was diagnosed as having cyclosporine nephropathy on the basis of one sclerose glomerulus, however, this data we feel support the safety of and minimizing the risk of developing cyclosporine nephropathy if you do keep the dose below 5 mg/kg/day, and you do not allow the serum creatinine increase to exceed 30 percent.

[Slide.]

Now, the functional changes that we have described result in serum creatinine increases, and this slide illustrates, shown in red, the percentage of patients by week 24 who experienced more than 30 percent increase in serum creatinine, and those who experienced more than 50 percent increase in serum creatinine.

In the dose group we are looking at, 2.5 to 4, we can see that over this period, 43 percent of patients will experience a greater than 30 percent increase in their serum creatinine, and this compares with 22 percent of patients who will develop a more than 50 percent increase in the serum creatinine. In the other boxes here, we see the incidences for the less than 2.5, maximum dose group, and the greater than 4 maximum dose group.

[Slide.]

Similar results were seen in Study 654, where there was a little bit more of a dose response seen, where we can see that in the 2.5 to 4.0 mg/kg/day dose range group, 57 percent of patients developed a more than 30 percent increase compared with 27 percent developing more than 50 percent increase.

[Slide.]

This slide illustrates the effect of nonsteroidal use

on the development of elevations of serum creatinine, with the Sandimmune group being shown in orange, and the placebo group being shown in blue.

In terms of patients developing greater than 30 percent increase in serum creatinine, for the Sandimmune group, more patients, 48 percent versus 31 percent of patients who received nonsteroidals developed more than 30 percent elevations, suggesting that perhaps these patients were slightly at greater risk of developing a more than 30 percent elevation. It should be noted the placebo group also showed a slightly greater increase, but the difference here was only 6 percent. And a similar picture was seen for a greater than 50 percent increase for the patients on nonsteroidals did appear to have a higher risk of developing a more than 30 percent increase in their serum creatinine levels.

[Slide.]

This slide illustrates what happens to serum creatinine over time in a cohort of patients who were followed out to a period of 24 months. To orientate you to this graph, these vertical lines represent the standard deviations, and the numbers in brackets above the lines represent the number of patients.

We can see that the serum creatinine rose from baseline

and stabilized around 12 months, and remained stable for the remaining duration of the time, with a rise of about 0.15 mg/dl. You will note, however, that the number of patients diminishes considerably over this period of time. So, what we have done is take a look at the 129 patients who were followed up for the entire two-year period, and that is illustrated on this graph.

[Slide.]

Again, we can see that after an early initial rise in serum creatinine, there does seem to be an appearance where the serum creatinine can maintain stably, and at the end point here, the mean rise above baseline was 0.15 mg/dl.

[Slide.]

Now, when patients do get this more than 30 percent increase above baseline serum creatinine -- which you see occurs between 40 and 50 percent of patients -- the physicians are instructed to reduce the dose of cyclosporine to maintain the level at less than 30 percent on the basis of the biopsy data we showed up.

This slide looks at the success of that maneuver and patients being able to achieve a less than 30 percent elevation of serum creatinine while still receiving cyclosporine therapy. So, this looks at patients who are on cyclosporine, developed a more than 30 percent increase, who

had a dose decrease, and looks at the effectiveness of that, and we can see that for both the Sandimmune and the Neoral groups, between 70 and 80 percent of patients do achieve on-drug reversibility of serum creatinine to take it back down below 30 percent and allow the patient to remain on therapy, indicating the success of this maneuver.

[Slide.]

Now, what happens to the serum creatinine levels that we have shown you become elevated while the patients are receiving cyclosporine?

[Slide.]

This looks at the follow-up population who participated in Study 302, the Neoral versus Sandimmune study. In orienting you to this graph, Neoral is shown in green, and Sandimmune is shown in orange. We can see that on this side of the line represents what happened in the clinical study portion while the patient was on drug, and this slide shows you what happens to the patient once cyclosporine therapy was withdrawn.

We can see that while on therapy, the serum creatinine level peaked at about 1.2 mg/dl, and even while on therapy, could be managed down to a slightly lower level. When the patient discontinued therapy for both the Sandimmune and the Neoral arms, you can see that the serum creatinine level

reduced, and indeed by end point the mean increase in serum creatinine above baseline was only 0.05 mg/dl above the baseline level, indicating almost complete reversibility of the renal dysfunction that was seen.

[Slide.]

This slide looks at reversibility of serum creatinine elevations in this population of patients. In Study 302, of the 91 patients, a total of 41 patients developed a serum creatinine increase greater than 30 percent at any time point, and these patients were followed to identify whether they reversed.

Reversibility was defined as serum creatinine returning to within 15 percent of baseline with all subsequent levels being less than 30 percent above baseline. Of the total number of patients, 33 of the 41 did achieve this definition of reversibility, that is, the return to less than 15 percent of baseline.

All but one patient of this 41 returned to within 30 percent of their baseline level over this period of follow-up. The 50 patients who are missing from this analysis of 91 never had a serum creatinine increase more than 50 percent above baseline.

[Slide.]

A logistic regression was conducted on this particular

cohort of patients to look for which factors might affect reversibility, and the following were not found to be associated with the degree of reversibility, and that would include the patient's baseline serum creatinine, the maximum dosage and duration of exposure, patient age, patient's sex, body weight, and concomitant nonsteroidal antiinflammatory drug use.

However, the factor that was found to have a significant impact on reversibility was the maximum on-treatment serum creatinine level, and this data is illustrated in this slide.

[Slide.]

Looking at a number of these risk factors shown on this axis with the percent change in serum creatinine above baseline at end point of follow-up.

We can see that the months on cyclosporine therapy, shown by these divisions, less than 6, 6 to less than 12, and 12 to less than 24 months, had no impact on the percent change in serum creatinine at the follow-up, nor did baseline serum creatinine level.

The one factor that was found to be associated was the maximum serum creatinine increase where we can see that if the serum creatinine increase was less than 50 percent and less than 30 percent, the residual increase in serum

creatinine above baseline was extremely low. As the maximum serum creatinine increase was allowed to rise, so, too, did the percent change in serum creatinine at the end of follow-up, again emphasizing the importance of if a patient achieves a more than 30 percent above baseline level, they should reduce a dose reduction.

[Slide.]

So, in summary, then, for the cyclosporine renal dysfunction, a modest serum creatinine increase is common. Serum creatinine increase has been shown to be dose-dependent. The serum creatinine can be stable over two years if the dose is adjusted appropriately. We have also shown that it can be reversible with the appropriate dose decreases.

[Slide.]

In terms of post-cyclosporine therapy, the creatinine increases are largely reversible with 33 of 41 of the at-risk patients returning to less than 15 percent elevation from baseline with all subsequent levels being less than 30 percent; 40 of 41 returning to levels of less than 30 percent above baseline; and the 50 remaining patients, as I stated, never achieving a more than 50 percent elevation above baseline at any time while receiving cyclosporine therapy. The reversibility is partial in some patients,

particularly when the serum creatinine increase is allowed to reach over 50 percent.

[Slide.]

In terms of our recommendations for Neoral use that has been based on this data, it is our recommendation that prior to initiating Neoral, that two baseline serum creatinine levels are obtained, that Neoral is initiated at a dose of 2.5 mg/kg/day. The serum creatinine be monitored over two weeks for the first three months, then monthly thereafter, and that the Neoral dose should be reduced by 25 to 50 percent if the serum creatinine levels exceed more than 30 percent above baseline.

If the patients get a change in nonsteroidal antiinflammatory drug dose or nonsteroidal therapy is introduced, then, the frequency of monitoring should be increased until it is determined that the patient has not experienced any adverse effects of that.

We do not recommend that the dosage of 4 mg/kg/day be exceeded.

[Slide.]

Now, I would like to move on to the next special safety topic, which is hypertension. The majority of these studies, as we have shown you, were conducted in the late eighties or early nineties.

In our studies, the following definitions were used for hypertension: adverse event reporting and also the WHO definition from 1984, which suggested hypertension would be considered to be present if the systolic blood pressure exceeded 160 mm of mercury, and the diastolic blood pressure exceeded 95 mm of mercury.

More recently, the Fifth Joint National Committee in 1993 defined hypertension requiring intervention as systolic blood pressure greater than 140 mm of mercury, and diastolic blood pressure greater than 90 mm of mercury.

Given that this is today's current treatment practices, we have chosen to reanalyze and present our data to you today based on this 140/90 definition. In terms of how the protocols were stated, however, we did not advise intervention for hypertension until the blood pressure reached 160/95, so the only data I will present to you on that definition does relate to the interventions that occurred for hypertension and the success of those maneuvers in controlling blood pressure to target, and the target in those patients was to reduce it to less than 160/95.

[Slide.]

Now, cyclosporine-induced hypertension is felt to be due predominantly to intrarenal vasoconstriction and less so will be due to sympathetic nervous system stimulation. For

the transplant population, the treatment recommendations that are used there, renal vasodilator drugs such as calcium channel blockers are effective in managing the hypertension.

[Slide.]

Now, this slide illustrates the mean systolic and diastolic blood pressure comparing the Sandimmune and placebo groups who participated in Study 651, 652, and 2008.

Looking, first of all, at the systolic group, with the Sandimmune group shown in orange and the placebo group shown in blue, we can see that over the 24-week period, there is an increase in systolic blood pressure, going from 126 mm of mercury at baseline to 135 mm of mercury mean at week 24. The placebo group also showed an increase of about 3 mm of mercury. The difference between these two points was statistically significant.

The diastolic group in both treatment arms, both Sandimmune and placebo, did show a trend upwards although not as large as in the systolic group, and the difference between Sandimmune and placebo for diastolic hypertension was not statistically significant.

[Slide.]

This slide looks at the cumulative incidence of newly occurring hypertension, hypertension being defined, as I said, by 140/90. For this analysis, we excluded patients

who did enter the study with higher blood pressures than 140/90.

Again, Sandimmune is shown in orange, placebo shown in blue. We can see that the incidence of systolic hypertension was 33 percent in the Sandimmune group versus 22 percent in the placebo group, indicating a difference between Sandimmune and placebo of 11 percent.

A similar pattern was seen with diastolic hypertension, it occurred less frequently, and 19 percent in the Sandimmune group versus 8 percent in the placebo group, and again, a treatment difference here of about 11 percent between the Sandimmune and the placebo groups.

[Slide.]

If we look at what happens to mean blood pressure in Study 302, I think it is notable that over the period of time of these studies, the blood pressure in both groups did not rise as much as it did in Studies 651, 652, and 2008, perhaps indicating more active intervention for hypertension, and I will show you that data shortly.

Systolic blood pressure rose by a mean of 3 mm of mercury and diastolic blood pressure by a mean of 2 mm of mercury over the course of the studies.

Now, as I have mentioned, for the majority of our studies, we stated in the protocols that the physicians

intervene for two consecutive blood pressure readings of greater than 160 or greater than 95, which was the standard at the time the protocols were conducted.

I would like to show you the data on the interventions that occurred in the studies and the success of those interventions in returning blood pressure to less than 160/95.

One comment I would make before I go through this presentation is that what we have noted is that intervention level for hypertension was not complete across the studies. A number of patients who should have been treated for hypertension by the protocol definition did not receive treatment.

[Slide.]

Beginning, first of all, with Study 302, to orientate you to this slide, the number of patients who developed systolic blood pressure greater than 160 and a diastolic blood pressure greater than 95 for two consecutive visits was 18 in the Neoral arm and 19 in the Sandimmune arm.

Now, looking at those patients who were controlled hypertensives on entry, for how many developed, many of these patients were on baseline hypertensive medications, we have 5 in the Neoral arm and 2 in the Sandimmune arm.

Of these 5, only two of these patients received any

additional antihypertensive medications to try and control the blood pressure, and in one of these patients, blood pressure did return to less than 160/95. No patients in the Sandimmune arm received any intervention.

Of the patients who were not receiving antihypertensive medications who came into the study, who were one of these 18 patients who developed hypertension, five of them received intervention, predominantly calcium channel blockers in the study, in the Sandimmune arm, and 71 percent returned to blood pressure readings of less than 160/95.

Similarly, on the Sandimmune arm, of the nine patients who required or received new antihypertensives, the blood pressure was reduced to less than 160/95 in six of these patients, a total of 67 percent, indicating the success of treatment in controlling hypertension in this particular study in the majority of patients.

Now, looking at Studies 651, 652, 2008, and 654, looking at the same orientation, again, we can see that lower numbers of patients except in Study 2008 who developed hypertension. Again, the number of patients on baseline antihypertensives was low. In Study 651, where most patients had the intervention, 50 percent of patients successfully returned to 160/95 blood pressure.

In the patients who were not receiving antihypertensive

medication on entry, who did receive treatment for it, across the studies, 0 percent in this particular study, but approximately 70 percent of patients who did receive intervention to control their hypertension were able to be maintained at the target blood pressure. In these particular studies, the majority of patients received beta blockers.

[Slide.]

Now, we have analyzed the risk factors for the development of newly occurring hypertension by both of the definitions that we have used.

First of all, looking at the patients who had a baseline blood pressure of less than 140/90, who developed either a systolic greater than 140 or a diastolic greater or equal to 90, and the significant risk factors were found to be baseline systolic blood pressure on Sandimmune treatment and baseline diastolic blood pressure on Sandimmune treatment for diastolic.

In terms of the patients who entered the study with less than 160/95 blood pressure, who developed hypertension, similar factors were found to be present, baseline systolic blood pressure and baseline diastolic blood pressure in the presence of Sandimmune therapy.

[Slide.]

In Study 302, a slightly different pattern was seen where for systolic blood pressure, the risk factor was also found to be age with no risk factors being identified for diastolic blood pressure for this analysis, and again for the less than 140 going to greater than 140, age was found to be the major risk factor, as well as baseline blood pressure.

[Slide.]

Now, we have taken a look at the two different types of patients in the studies, those who entered the study with a blood pressure of less than 140 and those who entered the study with a blood pressure of greater than 140, and if I can orientate you to the bottom half of this graph, again, with the Sandimmune group shown in orange and the placebo group in blue, we can see that for those patients who entered the study with a blood pressure of less than 140, they really could be maintained at fairly stable levels with minimal elevation throughout the course of the study, and this difference is approaching, but does not achieve statistically significance.

The patients who entered the study with blood pressures of greater than 140 did show more rise in their systolic blood pressure versus a fairly stable placebo group, and this difference was statistically significant.

[Slide.]

A similar picture was seen for diastolic blood pressure.

[Slide.]

Now, what happens to hypertension when cyclosporine is withdrawn? Again, looking at this reversibility. This slide summarizes an analysis that was done in the patients who went through the washout, the taper and washout in Study 651 and 652, and plots the change in blood pressure -- and this is systolic blood pressure -- over time in the study at treatment end point and at the end of washout.

At treatment end point, the mean increase in systolic blood pressure was 6 mm of mercury, and by the end of this four-week washout period, had fallen to 3.5 mm of mercury above the baseline levels.

[Slide.]

Similarly, for diastolic hypertension, the treatment end point, the blood pressure was 3.5 mm of mercury above baseline, and by the four-week follow-up, had returned to a mean of 1 mm of mercury above the baseline.

[Slide.]

So, in terms of hypertension, then, to summarize, we find that the incidence of newly occurring hypertension, defined as systolic blood pressure greater than 140 or

diastolic greater than 90, was 11 percent higher in the cyclosporine-treated patients than the placebo-treated patients.

Blood pressure levels could be maintained at less than 160/95 in the majority of patients who received interventions to keep them at that level of less than 160/95. We found that the patients who were over 65 years of age, who had higher blood pressure at baseline, are at greatest risk for developing an increased blood pressure with cyclosporine.

[Slide.]

In terms of our recommendations for Neoral usage, then, we would recommend that patients should have a blood pressure of less than 140/90, controlled by antihypertensive medications if necessary, before Neoral therapy is initiated.

If the blood pressure exceeds 140/90, antihypertensive medications such as calcium channel blockers, beta blockers, these were studied in our clinical study program, although other treatments are used in the transplant population, these therapies should be initiated.

[Slide.]

Finally, I would like to describe lymphoma.

[Slide.]

This slide summarizes the total number of malignancies that have occurred and been reported to Novartis either during or after completion of the cyclosporine clinical trials.

We can see that the most common tumor has been 10 patients with basal cell carcinoma, but I would like to orientate the discussion now to discussing the lymphoma incidence.

We had 3 patients in 1,968 treated patients who have been followed up for a mean of 6.5 years. We have done a calculation to try and estimate how this incidence compares with other reported series in the literature, and have found that this does not appear to exceed what might be expected in an RA population, and particularly in an RA population treated with immunosuppressant drugs.

[Slide.]

Now, I have mentioned three cases occurred in the clinical trials. For completeness sake, this slide summarizes all reports to Novartis which also includes three cases that have been reported in the commercial experience.

We estimate that more than 20,000 patients have been exposed to cyclosporine in the commercial experience, so three lymphomas occurred in clinical studies and three in commercial experience.

The duration of Sandimmune treatment is shown here, and it ranged from about three months in this particular patient to 46 months in this patient. There were three cases of B-cell lymphoma, one non-Hodgkin's lymphoblastic leukemia, and two Hodgkin's with mixed cellularity.

It is of note that of two of the cases in commercial experience, the patient was receiving concomitant methotrexate with the cyclosporine. This case reported in the literature from Italy and a recent report to Novartis from a patient treated in Finland with methotrexate, gold, and prednisone in addition to their cyclosporine.

[Slide.]

In terms of our recommendations for lymphoma, we would say that patients should be very carefully evaluated for the presence of malignancy before initiating and during treatment with Neoral, and patients with malignancy should not receive Neoral therapy.

The risk of lymphoma with cyclosporine does not appear increased over that expected for RA patients or seen for RA patients treated with other immunosuppressant drugs.

[Slide.]

To wrap up this safety presentation, cyclosporine therapy is most commonly associated with serum creatinine increase, nausea, abdominal pain, headache, and

hypertrichosis.

Although not presented, it is in your briefing book, we did not see any difference between the incidence of clinically notable abnormalities between Sandimmune and placebo with the exception of the renal function abnormalities.

[Slide.]

In terms of the renal safety summary, elevations of serum creatinine do occur commonly while cyclosporine-associated renal structural changes are rare.

Elevations of serum creatinine levels are, however, reversible after a decrease in dose in the majority of patients. The structural changes are infrequent if the dose is kept below 5 mg/kg/day and the serum creatinine is maintained at less than 30 percent above baseline level.

[Slide.]

Hypertension. The incidence of newly occurring hypertension occurred in 11 percent higher frequency in cyclosporine-treated patients than in the placebo-treated patients, and it could be managed in the majority of patients by the introduction of pharmacological therapy, such as calcium channel blockers and beta blockers.

For those patients who were receiving antihypertensive treatment on entry into the study, who developed worsening

hypertension, again, for those patients who received interventions, the majority could be maintained on cyclosporine.

Lymphoma. the risk of lymphoma with cyclosporine therapy seemed to be similar to that reported in the Mayo Clinic series in patients receiving slow antirheumatic drugs -- I am sorry, that is incorrect -- very similar to that reported in the literature in RA patients and in RA patients receiving immunosuppressant therapy.

Also, we have demonstrated that patients have safely maintain on cyclosporine therapy for periods up to two years.

I think I should pause here before getting into the combination therapy, pharmacokinetic interaction for any questions.

DR. PETRI: Dr. Torley, let me start by asking, you have discussed these major problems, the renal and the hypertension, as separate entities. How often are they going to occur together, in terms of labeling if a patient has new hypertension, currently, you would not recommend that there be a dose reduction in the cyclosporine, is that correct?

DR. TORLEY: That is correct.

DR. PETRI: Can you justify that?

DR. TORLEY: Could I go back to the other microphone?
I have my slides, the evidence for that up over there.

DR. PETRI: So there will not be any patients who have both the increase in creatinine and the hypertension occur together?

DR. TORLEY: There certainly are, but the two can occur separately, and that is why we make the recommendation that the serum creatinine is dealt with separately from the hypertension, because there will be a proportion of patients in whom the hypertension develops who do not develop these greater than 30 percent increases in the serum creatinine.

DR. PETRI: Let me follow that by the physician treating the hypertension with calcium channel blockers, there is then going to be an interaction with dosage level. Can you comment on that?

DR. TORLEY: We would advise against the use of the calcium channel blockers that interfere with cyclosporine levels. These include nicardipine, diltiazem, and verapamil. The other calcium channel blockers have not been shown to have an interaction, and those are the calcium channel blockers we recommend are used.

DR. PETRI: So you believe that should be part of the labeling?

DR. TORLEY: Yes, it is proposed.

DR. PETRI: Let me ask for questions from the panel.

Dr. Felson.

DR. FELSON: Let me ask you a little bit about the lymphoma risk. You were careful in your comparability statements, and I wanted to just query you a little bit about comparing the risk of lymphoma in cyclosporine-treated patients to, say, the risk in Mayo Clinic all RA patients. What is the difference? I realize the numbers here are 3 per 2,000. It is actually, probably 3 per 2,000 person years or something like that.

DR. TORLEY: It is more than that.

DR. FELSON: Those numbers are fairly small.

DR. TORLEY: Right.

DR. FELSON: But how does that compare to Mayo, and I also wonder if you would comment on the risk of lymphoma when this drug is used to treat transplant patients.

DR. TORLEY: I would like to invite Dr. Brian Strom up to present the data.

DR. STROM: Can I have my slide 6, please. This relates to the question of lymphoma compared to Mayo Clinic series specifically, not the transplant experience.

[Slide.]

As you can see, as indicated, there were three cases in or after the clinical trial exposure. There was a total of

6.6 years per patients to follow-up in the 1968 patients in the clinical trial experience, so that is 0.00023 cases per year.

Using population-based data from Mayo Clinic, 1950 to 1975, all 521 new RA patients, the rates in females that were observed were 0.00038, the rates in males were 0.00028 cases per year, so very similar to RA in general.

[Slide.]

In addition, using newer data from Mayo Clinic, there were 39 cases diagnosed over 16 years in RA patients on DMARDS, 16,000 patients over the 16 years. If you assumed, therefore, eight years of follow-up, if you assumed 20 percent were on DMARDS, it gives a rate of 0.0015 cases per year on DMARDS; if you assumed 33 percent of the patients were on DMARDS, because the Mayo Clinic gets the referral population, that is 0.009 cases per year.

So, the rates observed in the clinical trials experience are equivalent to that Mayo Clinic sees in RA in general, and actually potentially even lower, subject, obviously to extrapolations and the small sample size.

DR. FELSON: Can you go back to the previous slide for a minute? It is rather striking that these people that you are following are on for 6.6 years per patient. I didn't see any of the trials that were anywhere near that long.

What is that?

DR. STROM: That is time -- what I did in calculating the 6.6 years is take the start date of the study, that is, when the first patient was enrolled, the end date of the study when the last patient was enrolled, take the mid-point of the study, the mid-point between those two and carry that through December 1996, again on the assumption that --

DR. FELSON: This is a follow-up of patients who at one point were exposed to cyclosporine, but did not, in fact, have 6.6 years of exposure.

DR. STROM: Exactly.

DR. FELSON: They could have had six weeks of exposure, and you are following them. As a matter of fact, many of them did have six or 12 or 24 weeks of exposure, and you are following them for six years to see if they develop lymphoma and looking at that rate.

DR. STROM: Exactly, and that is where the three comes from. It is a follow-up that is of all patients ever in the clinical trial experience, how many have since been diagnosed with lymphoma.

DR. FELSON: Can you comment also on the transplant experience with lymphoma or leukemia, or any related malignancies?

DR. TORLEY: Dr. John Curtis, who is a transplant

physician and surgeon, will comment.

DR. CURTIS: The incidence of lymphoma is higher than would be expected in transplant patients, in our population, about less than 1 percent however have lymphoproliferative disease after transplant.

Israel Penn keeps a registry in Cincinnati, and while the incidence of lymphoma prior to cyclosporine was higher than expected, the introduction of cyclosporine in '83 did not seem to change this. There was, however, a spurt in the incidence with the introduction of additional drugs, which were used in transplant patients, the OKT3 monoclonal antibodies, and there has been within the community some concern about OKT3 extensive immunosuppression. The general feeling is a total dose of OKT3 triple drug immunosuppression, that the total dose of all immunosuppressants can lead to this.

Most of the lymphomas seen in the transplant community are B-cell lymphomas which fortunately, with discontinuation of immunosuppression, seem to resolve very nicely. However, some of them do on to mortality.

DR. PETRI: Dr. Liang.

DR. LIANG: Could I ask a related question? We have focused on lymphoma, but is there any data with respect to expected rates for the other malignancies that were

observed?

DR. CURTIS: In transplantation, basal cell carcinomas are also marked increased, cervical carcinoma is also increased, and these are rates that are higher than the lymphomas actually in our population.

DR. PETRI: Based on that, do you think that should be part of the labeling, increased surveillance for basal cell and cervical carcinoma? Cervical carcinoma would be a major issue because the majority of rheumatoid patients receiving this drug would be female.

DR. CURTIS: I would think it would be wise.

DR. PETRI: Dr. Liang, any follow-up?

DR. LIANG: And then you claim that you have 20,000 patients on cyclosporine worldwide. What is the information on toxicity, adverse events, in that group? I mean is there any?

DR. TORLEY: We arrived at the number of 20 percent based on -- I am sorry, 20,000 -- based on a survey done by the individual countries. In terms of adverse event reporting, this is very much by country. The physicians are instructed to obviously, when products are approved, to report to the sponsor, so we do collect the database of adverse events.

DR. LIANG: I understand that. What is the data?

DR. TORLEY: What is the data - in terms of lymphoma, you saw the three cases that have been reported in post-marketing surveillance. In terms of renal failure, we have not seen any additional cases of chronic renal failure, but we have had two reports of acute renal failure in the commercial experience.

The incidence that has been reported to us by post-marketing surveillance is no higher than that observed in the clinical studies as might be expected due to the underreporting in the post-marketing surveillance. We haven't seen anything untoward or newly emerging event that did not already occur in the clinical study experience.

DR. PETRI: Dr. Whelton.

DR. WHELTON: Thank you, Dr. Petri. I have a number of short-targeted questions for you, if I may, and I will start with a sequitur to Dr. Petri's question, and ask, in relationship to the hypertension issue and the pathophysiological mechanisms, do you have pretreatment renin angiotensin profiling data and posttreatment data insofar as a putative but important mechanism in the development of the hypertension is the intrarenal vascular effects? That is Issue No. 1.

DR. TORLEY: No, we do not in this rheumatoid arthritis population. Would you like to hear about the evidence in

the transplant populations, would that be relevant?

DR. WHELTON: No. These are targeted questions.

The next issue is are 24-hour monitoring, blood pressure monitoring data available to define is the effect during the active impact of cyclosporine, or is there a change during the nocturnal phase of the blood pressure?

DR. TORLEY: We have never done 24-hour blood pressure monitoring.

DR. WHELTON: I will now go back to the start. I look that one, Michelle, out of sequence as a follow-up to your question.

Starting with your definition, the rule of thumb for serum creatinine at 30 percent increment, which then should put into operation possible reduction of the drug, was that a retrospectively developed rule of thumb or a prospective one? I bring this up because in dealing with an average patient, let's say, starting with a serum creatinine of 1, and on the next determination, if the creatinine is 1.3, that is a 30 percent increment.

In fact, that change, based on the standard methodology used in autoanalyzer equipment, the alkaline PK rate methodology, that just brings that barely within 95 percent confidence limits that that is a real change.

Now, you have told us that you are recommending two

baseline serum creatinine determinations. What do you recommend, then, at six months, when a creatinine on an outpatient basis is found to have gone from 1 to 1.3?

DR. TORLEY: To answer the first question that you asked, that 30 percent level was arrived at retrospectively based on the biopsy data I showed you to limit any morphological changes.

According to how our protocols have been conducted, we have instructed a reduction arm, understanding the limitations of the methodology, if the patient's creatinine exceeds 30 percent, they should have a dose reduction with patient safety being our biggest concern here, and taking a very conservative course.

DR. WHELTON: Now, was that built in, in the prospective trial data, was that built in as a protocol mandate?

DR. TORLEY: Yes.

DR. WHELTON: Then, what percentage of people were protocol violators if they went greater than 30 percent and didn't have the reduction?

DR. TORLEY: I don't have that number to hand, but when we initiate these protocols, we spent a fair amount of time in instructing the physicians on the importance of it and the potential adverse consequences.

I would say there will have been patients who violated that. I know that if physicians felt the patients were getting a great benefit, and it was on the cusp, I could imagine they might not reduce the dose, but we certainly strongly advise that you do reduce.

DR. WHELTON: I commend you on these issues having been at the bedside trying to make these difficult decisions myself, so I just point out that that is right at the grey zone when you comparing statistical significance.

DR. APPEL: Andy, I would like a shot at answering that question. I am Dr. Gerald Appel. I run Clinical Nephrology at Columbia Presbyterian.

My background experience with cyclosporine is fairly extensive. My group follows about 500 renal transplant patients of which I follow approximately 100, which the vast majority are on cyclosporine. I have started several hundred nephrotic patients on cyclosporine over the years. We are part of the North American collaborative trial on cyclosporine for focal sclerosis and for membranous nephropathy, and we have published our experience using it in lupus patients, for membranous lupus and for diffuse proliferative disease.

I absolutely agree with Andy's comments. In fact, we were discussing this at length over the last several days,

that I could make a scenario that is even more dramatic. Take the person whose creatinine is 0.6 to start, and they go a 30 percent rise to 0.8, well, that is within the area of the autoanalyzer 0.2, so really you are getting down to points which are very hard to measure, but the company has decided to take the most conservative route and say that, yes, we will sacrifice potential efficacy for safety in this matter, that in clinical practice, if somebody went to 0.6 to 0.8, I probably would continue the medication myself. So, this is a very conservative approach in terms of trying to prevent toxicity.

DR. PETRI: Dr. Appel, while you are still at the microphone, I would like to ask a follow-up question. We are concentrating right now on the limits of autoanalyzers, but the operational rule of a 30 percent increase in creatinine ignores everything we know about how to best watch over a patient who is at risk for tubular interstitial disease, namely, that tubular secretion of creatinine is going to affect the serum creatinine and the creatinine clearance, and I think that has, in fact, been proven for cyclosporine, that a better measure, such as a technetium DTPA clearance or an iothalamate clearance, may show that there are patients who are at risk, who still have normal serum creatinines.

Can you comment on that? Has that been introduced into this discussion?

DR. APPEL: That is an important area, Michelle, because I think you have to separate in your mind the functional effects and the morphologic effects. Morphologically, there is no doubt that long-term we are interested in tubular interstitial fibrosis and scarring as a problem that may reduce function over years or over many months.

In the short term, the rising creatinine is probably related to renal vasoconstriction and unrelated in any way to the morphologic changes. It just predicts if you have this vasoconstriction and a rise in creatinine, it predicts the people who are going to go on and develop interstitial fibrosis.

This is taken, of course, from Feutran's paper in The New England Journal on the 192 patients and a number of other studies. So, based on that, we are really saying that it is not the tubular interstitial disease once it is there we are trying to discover, it is trying to prevent it by preventing the vasoconstriction which leads to this.

DR. PETRI: But in your view, the literature would prove that this 30 percent operational rule would be sufficient to prevent important tubular interstitial

disease.

DR. APPEL: That is correct, yes, even more so. I would think 50 percent would have been a better guess.

DR. PETRI: Dr. Whelton has a follow-up.

DR. WHELTON: While you are still at the phone, Dr. Appel, to move on to the issue of the tubulointerstitial process, granted, we know mechanistically, there are glomerular impacts, there are tubular impacts, but in terms of the slow, progressive nephropathy that evolves, it is dominantly a chronic tubulointerstitial process.

Much of the data you have shown us, and very elegant although they are, get out as far as month 24, and the next dot is greater than 24. Since the progression of chronic tubulointerstitial nephropathy is a 10 to 20-year phenomena, although I am looking this way, I will now turn to Dr. Appel and ask Jerry, Jerry, what data are available on this issue of slow progression?

We were led to believe sort of that there was a plateauing at 12 to 24 months. What are available longer?

DR. APPEL: From the autoimmune disease population, I can tell you I have very little data. Even in our own studies, we just have not followed patients that long.

In terms of the transplant data, we analyzed our data at Columbia Presbyterian on over 500 heart transplant

patients who have been followed long term, and we have looked at our renal data, and in general, there is a decrease in function and then a stabilization, but some patients do go on to develop interstitial scarring over a long, long period of time, and many people feel if you go out at 10 years, that is where the curve will pick up, but we just do not have the data.

In fact, the data is just getting there in terms of transplant, that I have a feeling that most of the panel is rheumatologists, if they could get their patients healthy for 10 or 15 years, they would be very happy with one medication. Nevertheless, this is a concern long term with any of these medications, that long-term toxicity will build up.

DR. PETRI: Dr. Appel, I would like to ask you to stay at the microphone for the next question, but, Dr. Torley, please address it, as well.

Don't you have enough data to do some subgroup analyses of the different NSAIDs? This is going to be a concern in labeling because the great majority of the rheumatoid patients, who will be on Neoral, will also be on NSAIDs, and you have shown us a concern that the use of NSAIDs may be increase the risk of the creatinine increase.

DR. TORLEY: We have done multiple subgroup analysis, I

must admit not broken down by individual NSAIDs. We compared the incidence of adverse events depending on if you were on an NSAID and not, and found no difference.

Again, hypertension we not found to be significantly affected by being on an NSAID versus not. Serum creatinine increase did seem to be more common. The only subgroup we have looked at in terms of NSAIDs is diclofenac because of the pharmacokinetic interaction between diclofenac and cyclosporine that has been demonstrated.

DR. PETRI: I would like to ask you, Dr. Appel, and also Dr. Whelton, if you want to comment, on potential interactions in different NSAIDs.

DR. APPEL: Well, first, let me say this was the most surprising thing to me in looking at the data, that there wasn't an increased incidence of nephrotoxicity or a rise in creatinine with the NSAIDs, a statistically significant incidence, because I would have expected it, and there is some data to support this, and I still think that the combination should be used carefully.

Nevertheless, the monitoring guidelines here are much stricter than what are used or suggested, are much stricter than what is used in general for many other populations. I think the nephrology community is aware that the transplant population, once they are stable, they are followed every

three months with usually blood tests. I know John Curtis does that at probably the largest transplant center in the country, in Birmingham. We do that at Columbia Presbyterian. Our stable patients are followed every three months with creatinine, it is not every month. So, this population is clearly going to be followed even when stable much more closely.

But in terms of individual agents, that has turned out to be a bag of worms certainly for nephrologists, and I think there is at least as much expertise on the panel in terms of whether difference NSAIDs are more nephrotoxic than others than there is in the nephrology community.

DR. PETRI: Specifically, the labeling is going to recommend that a change in NSAID means more frequent monitoring of creatinine. Is that necessary?

DR. APPEL: I think it is a good idea. I mean nobody can argue with more frequent monitoring. I mean you can say it costs more, but in terms of being cautious in terms of with two potentially nephrotoxic agents, I think, you know, I am in favor of it.

DR. PETRI: I guess I am asking were there data that led to that recommendation.

DR. APPEL: Not data that I know of.

DR. TORLEY: I would comment that it was simply on the

slide that I did show in my presentation, that it did show that patients who are receiving concomitant NSAIDs are at great risk of developing more than 30 percent increase, and from that it was extrapolated that if you changed the NSAID or increased the dose, perhaps the patient would be at accelerated risk of getting more than a 30 percent increase.

DR. PETRI: Dr. Whelton.

DR. WHELTON: I think that finding of not seeing the interaction with nonsteroidals, although on the surface a little surprising on cogitating on it further, I think it does fit in with the general body of information that we know.

When somebody is rendered susceptible to the potential for further deterioration of renal function by a nonsteroidal, just taking the renal functional issue as a separate risk factor, it isn't until the serum creatinine exceeds 2.2 based on much of the available published data that such patients are at risk.

So, I wondered as I read through the materials before the meeting whether there were enough patients for subset analyses to cull out those who had a baseline creatinine exceeding 2, who then had the addition of a nonsteroidal, and I would suspect in that group, there may have been some interaction.

DR. TORLEY: We actually restricted entry to our studies with patients with normal function defined differently by the various protocols, but an average, a maximum of 1.5 mg/dl for males. So, we don't have a population of patients.

DR. WHELTON: I would think when it comes to a labeling issue, it is particularly those who have mild preexisting renal impairment are going to be the ones particularly at risk to this interaction, and I am absolutely sure it will be seen.

DR. APPEL: I would be most cautious in using cyclosporine in patients with a nontransplant condition with creatinines that are in the range of 2 or 3. In general, when we have done this nephrotic patients or lupus patients, we have often had significant rises in the creatinine, so I generally would try to use them in patients with better preserved renal function.

DR. PETRI: Dr. Johnson.

DR. JOHNSON: Some of the earlier clinical protocols did allow creatinine bumps beyond 30 percent, in fact, most of them did, and the one that allowed it the most was 2008, which was designed at 85, I think, and that allowed a bump up to 75 percent. If you look at the risk, the cumulative risk of a creatinine increase of 30 percent or 50 percent,

or something like that, you know, it starts kicking in at around 30 percent at a dose of 4 mg, and it really shoots up at a dose of 5 mg.

Correct me if I am wrong, but I think this was part of your thought process that it is sort of the history of the dosing strategy.

DR. TORLEY: Yes, exactly.

DR. PETRI: Dr. Simon.

DR. SIMON: I would like to pursue this line of discussion a little bit farther because I am a little confused. If we do understand that the kidney effects are partly modulated through alterations in glomerular filtration rate due to renal vascular changes, and we do know, Dr. Whelton, that the changes in nonsteroidals are partly related to predisposed patients who have decreased renal plasma flow, that the combination seems to be putting that patient particularly at risk. That is number one.

Number two, I am a little concerned in the discussion regarding the amount of risk that a patient with a serum creatinine at 2 or 2.2 might have. Given the fact that rheumatoid arthritis patients tend to be debilitated and small, lower body mass, and particularly might be walking around with a serum creatinine of 1.7, which would be equivalent to a serum creatinine of 2.2 or 2.5 in somebody

who otherwise was healthy, thus, I am a little concerned about the lack of specificity that serum creatinine tells us as opposed to creatinine clearances or other forms of renal testing that have already been alluded to.

If, indeed, the renal experts think that the amount of creatinine clearance or what is going on in the serum creatinine would preclude the use, I wonder whether or not we should actually be even more conservative and in the labeling recommend that someone with long-term rheumatoid arthritis, since that is what we are talking about here, very sick people, who have a serum creatinine of 1.7, should be the ones that we are very worried about.

That leads me to my third question, which has to do with your dosing schedule, which is per kilogram. I wondered if this was lean body mass, not lean body mass, and how you determined per kilogram related to that.

DR. TORLEY: I have to start with the last question. The protocol simply stated that patients could not be obese to come into the study. We just took their actual weight on the clinic scales to dose them, so it wasn't lean body mass or anything like that. It was just their actual weight by which they are doses in our clinical studies.

DR. JOHNSON: Why did you choose not to have obese patients? What was the story behind excluding those

patients?

DR. TORLEY: I have to say that was before my history in the program. I am not clear on that, but I noted when I was reviewing the inclusion/exclusion of these patients, which was not defined, were excluded from our studies.

DR. JOHNSON: So, you are suggesting that the way you determined the dose would be based on whatever the body weight is as determined at that visit, and that you would not determine it based on what projected lean body mass would be?

DR. TORLEY: The data I showed you was collected in that manner.

DR. JOHNSON: Okay. And then the other questions related to the choice of where we would worry, and then the pathophysiology I wondered about.

DR. TORLEY: I think at this point we state in the proposed package insert patients with normal renal function. I think it has been very difficult with the different types of patients, a male patient versus a small, elderly female patient, to come up with an exact cutoff that could be easily understood, but we certainly would be open to coming up with whatever definition of normal renal function would be present.

DR. PETRI: I believe Dr. Appel wanted to comment at

this point.

DR. APPEL: Just one comment on the lean body mass. One area where this is relevant is in the nephrotic patient who has a large amount of edema. There, in general, I have used lean body mass because these people can diurese over a couple of weeks 30, 35 pounds, and it is obviously salt and water, and not relevant to their dose of cyclosporine.

In terms of other testing techniques, we have not found clearance techniques to be helpful in terms of better than the serum creatinine, and this includes not only creatinine clearance, but iothalamate clearances. They were part of the North American collaborative trial for nephrotics and for focal sclerosis, and membranous, and they were dropped because they were coming out the same as the creatinine clearance, and no better than the Cockcroft Gault formula using the serum creatinine because of the variability in collection. Even iothalamate clearances, the variability was just too great.

So, I think in terms of a reliable test, probably because of collection variables, and especially for practicing physicians, I think a serum test is clearly the answer.

DR. PETRI: Dr. Torley, I am not sure we sufficiently addressed Dr. Simon's question because

corticosteroid-induced adiposity is going to be a problem in many long-term rheumatoid patients.

Do you have other consultants present who might address that further?

DR. TORLEY: Any volunteers to address that question?

DR. YOCUM: Dave Yocum, University of Arizona.

In the protocols which I was with before Helen came onboard, we were concerned about the absorption of cyclosporine into fat tissue, and there were some reports of excessively large patients who had excessive rises in serum creatinines, so that the decision in Novartis now was to exclude "obese patients," but I must say there were patients who were listed as overweight, who still were treated.

I can say that it was really not a major issue. I must say that there is edema in, what, about 5 percent I think, Helen, of patients on cyclosporine that we do see, and in my clinical experience again over the years, it has not made a difference, but again, I think it would have to be taken into account. How you deal with that labeling, I am not sure.

DR. PETRI: We have lots of comments here. Dr. Abramson first.

DR. ABRAMSON: I just have a couple of questions. One is you haven't addressed serum levels. I know some

physicians use serum levels in following patients. What is your opinion of the value of that in toxicity and efficacy?

DR. TORLEY: Serum trough levels were -- Study 653 was conducted particularly to look at whether trough levels might be useful in determining the appropriate dose of cyclosporine. In Study 653, what we saw was there was no correlation either in efficacy or in the major safety parameters of change in creatinine, change in blood pressure between trough levels.

So, based on that, and a number of other observations, we have concluded trough level monitoring is not useful in this rheumatoid arthritis population.

DR. ABRAMSON: The other question I had was in the graph that you showed of people treated for I guess it's 24 months, and you had 126 people, and the issue of creatinine underestimating actual renal pathology, do you have more data on those patients, were they hypertensive, were there any signs of interstitial dysfunction with regard to electrolytes?

DR. TORLEY: I would say those patients are probably self-selected out to have not encountered any renal problems, that they were still on therapy, so no biopsies or anything like that were done. Those patients obviously could maintain their serum creatinine levels less than 30

percent to be able to be on the drug for two years.

DR. APPEL: In the 192 patients with autoimmune disease who were treated and published in that New England Journal article, hypertension was not a variable that factored in, in terms of nephrotoxicity, so that when they looked at the different factors, the rise in creatinine was, age was, but there was no relationship between hypertension.

DR. JOHNSON: A follow-up question in that regard. You also drew blood levels on 302, and they have now been unblinded. Did you look for predictive value of blood levels in that study?

DR. TORLEY: Yes, we did. Perhaps I can invite Dr. Choc, pharmacokineticist, to address that particular question.

DR. CHOC: Yes, we did look at trough levels, as well as in a small subset within 302, pharmacokinetic parameters, ACC Cmax and Cmin to try to relate them to safety and efficacy. The efficacy parameters were, of course, in this study confounded by the design in which doses were being lowered in response to safety parameters, but when we looked at the serum creatinine, blood pressure again we found that there were some correlations between trough, ACC Cmax and Cmin, but in general, that the predictive value of these correlations were generally quite low with most of the

correlations of R value of less than 0.3.

DR. PETRI: Felix has a question.

DR. FERNANDEZ-MADRID: On hypertension, my understanding is that the level of 160/95 was used to determine interventions to control the blood pressure, and we hear an 11 percent incidence of hypertension related to cyclosporine.

DR. TORLEY: Right

DR. FERNANDEZ-MADRID: Was this 11 percent related to the 160/95 or to 140/90?

DR. TORLEY: Actually, the protocol stated 160/95 was the definition of hypertension. We had about 11 percent of patients develop blood pressure levels greater than 160/95 using that definition. When we used the 140/90 definition, there was an 11 percent difference between the incidence in the Sandimmune group versus the placebo group, and that is why the 11 percent has been attributed. That is the difference between the Sandimmune group and the placebo group that appears attributable to treatment is the 11 percent difference.

DR. FERNANDEZ-MADRID: So, what was the incidence if you consider the 140/90?

DR. TORLEY: Including all patients, including those who entered the study with a blood pressure of greater than

140/90?

DR. FERNANDEZ-MADRID: Yes.

DR. TORLEY: It was over 50 percent.

DR. PETRI: Dr. Pucino.

DR. PUCINO: A follow-up to that question. In terms of the persistence of hypertension, 75 percent had blood pressures above 160/95. What percentage of patients had blood pressures above the 140/90 that persisted?

DR. TORLEY: I am sorry, I am not familiar.

DR. PUCINO: The data that you presented showed that 75 percent of the patients, the blood pressure returned to values less than --

DR. TORLEY: All right.

DR. PUCINO: What percentage of patients returned to under 140/90?

DR. TORLEY: I did a subset looking at the patients who entered the study with a blood pressure less than 140, who went to more than 140, and looked at those patients in whom an intervention happened to occur, and again it was a similar proportion of patients that did reverse, going to below 140/90.

If we look at the number of patients whose blood pressure went to over 160/95, very few of them got to 140/90 because that was not the treatment target. But if you

enter with a blood pressure of less than 140/90 and go to greater than 140/90, the calcium channel blockers and beta blockers were again effective in bringing the blood pressure below 140/90.

DR. PETRI: If there are no pressing panel questions, I would like to let Dr. Torley finish with her safety presentation.

[Slide.]

DR. TORLEY: One of the specific questions I believe the committee has been asked to address is whether there is a pharmacokinetic interaction between cyclosporine and methotrexate, and what are the clinical implications of that interaction. I would like to present to you some pharmacokinetic data and some clinical data for your consideration.

[Slide.]

Study 351 examined the pharmacokinetics of methotrexate, established the multiple-dose pharmacokinetics of cyclosporine after administration of Neoral, and then assessed whether there was any interaction between the pharmacokinetics of each when the two were co-administered.

In this study, which was an open-label study, 30 patients with RA were entered. Patients were on individualized doses of methotrexate, which they received on

days 1 and 23, and the Neoral, a total dose of 3 mg/kg/day was administered between days 8 and 23.

Pharmacokinetic profiles of methotrexate and 7-hydroxymethotrexate in plasma and urine were collected in days 1 to 3, and 23 to 25, and the pharmacokinetic profiles in cyclosporine were collected in days 22 and 23.

[Slide.]

This slide summarizes the effect of methotrexate on Neoral exposure in these rheumatoid arthritis patients, with the Neoral group shown in green and the methotrexate and the Neoral combination arm shown in gray. This looks at the AM dose and the PM dose of Neoral area under the curve, and we can see that when methotrexate is co-administered with cyclosporine, there is no effect on the cyclosporine pharmacokinetics in terms of the AUC in either the AM or the PM dose.

[Slide.]

Now, this slide looks at what happened to the methotrexate and the 7-hydroxymethotrexate levels when the cyclosporine was added. Again, similar orientation with the methotrexate in the Neoral arm being shown in green, and the methotrexate-alone arm being shown gray.

We can see that in terms of the area under the curve, when Neoral was co-administered with methotrexate, there was

a slight increase in AUC, which was an average 30 percent greater, so methotrexate AUC increased by 30 percent when Neoral was co-administered.

In contrast, the area under the curve for 7-hydroxymethotrexate was diminished by about 75 percent when the two were co-administered. It is important to note that the elimination of both products still appeared to occur along the same line with elimination of the product by the 24-hour period.

[Slide.]

Now, this is a study from Lafforgue which looked at the correlation between response of methotrexate and pharmacokinetics, and it is mirrored by several other publications and the literature which has not been extensively studied, but appears to demonstrate that no correlation between pharmacokinetics and degree of response to methotrexate.

In this study, which shows AUC, Cmax and CLR/F, we can see that between the responders, which were defined as patients having a 50 percent response in two of the four of swollen joint, tender joint, global, and MD global, there was no difference in either the AUC, Cmax or CLR/F in terms of whether the patient would respond or not.

[Slide.]

Now, we tried to determine what was the mechanism whereby the methotrexate area under the curve increased and the 7-hydroxy and methotrexate area under the curve decreased, and this slide looks at the difference in creatinine clearance in patients, and looked at the difference in methotrexate AUC, and we failed to demonstrate any correlation between a difference in creatinine clearance and the methotrexate area under the curve.

[Slide.]

A very similar picture was seen for the 7-hydroxymethotrexate where a difference in creatinine clearance did not appear to have any effect on the actual AUC.

[Slide.]

In summary, then, the combination of cyclosporine and methotrexate was found to be associated with a 30 percent increase in methotrexate area under the curve, and a mean 75 percent decrease in the 7-hydroxymethotrexate area under the curve.

In spite of an apparent decreased clearance of methotrexate, the plasma levels of methotrexate were not seen to persist beyond 24 hours. No correlation was seen between the change in creatinine clearance and the change in bioavailability of methotrexate or 7-hydroxy.

Finally, no correlation has been demonstrated that we are aware of between the methotrexate pharmacokinetic parameters and clinical response.

[Slide.]

Now, in terms of the clinical implications of this, our best example of where we can look for this is Study 654, which examined the co-administration of Sandimmune and methotrexate in a group of patients for 24 weeks.

We have looked at the adverse event rates between the patients receiving the combination and the patients receiving placebo and methotrexate, and also for comparison purposes, I have included the adverse event rates in the methotrexate-alone arm and the Sandimmune-alone arm from Study 651.

It is our conclusion that there was no newly occurring adverse events as a result of this, or there didn't appear to be any increased adverse events that could be attributable to enhanced methotrexate toxicity based on these data.

[Slide.]

Clearly, one also wants to look at laboratory analysis to see whether there is any additional toxicity, and this slide looks at the incidence of clinically notable laboratory abnormalities, the definition of which is shown

here, where platelets less than 100,000 were considered clinically significant and hemoglobin levels of less than 9.5 were considered clinically significant.

We can see a similar hematological profile between the two, and a similar picture was seen for white cell counts. If we look at biochemistry, obviously, the creatinine abnormalities were higher in the Sandimmune group, which we feel is attributable to the cyclosporine therapy.

Uric acid was a little bit higher in the combination arm, but magnesium levels clinically relevant lowered were not present. We have taken a look at SGOT and SGPT levels two ways. We looked at this clinically notable definition where there did not appear to be a difference between the two, but according to the ACR guidelines, we have also looked at the incidence of patients who developed elevation of the liver function tests, al phos, bilirubin, SGPT, and SGOT above the upper limit of normal for those individual laboratories.

We can see for alkaline phosphatase and for bilirubin there is a slightly higher incidence of patients developing at least one level outside the upper limit of normal in the combination arm versus the methotrexate and placebo arm. However, the opposite pattern is seen for SGOT and SGPT where more patients receiving methotrexate alone exceeded

the upper limit of normal than did our patients receiving the combination.

[Slide.]

So, in conclusion, although there was a pharmacokinetic interaction observed between methotrexate and cyclosporine, results from the six-month trial in which both drugs were co-administered has failed to reveal any adverse clinical implications.

Thank you.

DR. PETRI: Let me ask the panel for questions directed at this part of safety. Dr. Lovell.

DR. LOVELL: As I understand it, the maximum allowed methotrexate dose in your trials was 15 mg/week, is that correct?

DR. TORLEY: That is correct.

DR. LOVELL: I would like some comment from one of your consultants or from you about the problem that is going to happen with methotrexate creep and that a lot of adult patients are treated now I think in excess of 15 mg/week, and what interaction that might have clinically in the use of cyclosporine.

The other question I have is the labeling recommends periodic monitoring of uric acid, phosphorus, potassium, and in your data, although some of it was not even discussed,

that seems to be kind of a moot point, and I wonder what you thought about the requirement in labeling for monitoring of that problem.

DR. TORLEY: If I can address the first question, and Dr. Yocum will. At the time the combination study was conducted, it appeared that the general practice in the United States was not really to exceed a dose of 15 mg/week. Over the last four years, I would say we have seen the dose of methotrexate being used has increased.

We actually have a study ongoing at this time which allows patients to be entered into the study with doses of up to 20 mg, which is the maximum label dose of methotrexate, to try to gain data and address that issue.

David.

DR. YOCUM: Excuse me. The second question was what?

DR. TORLEY: The second question was why we recommend magnesium and uric acid monitoring given that we had very few patients with clinically notable differences.

DR. YOCUM: Again from my clinical experience over the past 13 years with this drug, especially at the lower doses, I actually don't think it is needed. There has been no association that I have seen with the problem.

Again, I think one would have to be concerned toward the first question of the rising methotrexate doses that are

now being used in adult patients, and I think that in that line, maybe this more close monitoring that has been suggested throughout the meeting so far is warranted and needed to make sure, because I think once this drug is begun to be used in general practice more, I think the company, as they have outlined, needs closer monitoring. While it is a cost issue, I think we are really looking at a safety issue here in delving into this area.

DR. LOVELL: Do you mean the monitoring that has been recommended for the labeling or the fact that the monitoring recommendations in the current labeling would be overly conservative for 15, but adequate for higher dosages?

DR. YOCUM: I think they are overly conservative for 15, but I think they are going to be adequate for the higher dosages.

DR. PETRI: Dr. Hochberg is at the microphone.

DR. HOCHBERG: Just to follow up, in my clinical experience with the combination, probably the majority of my patients who are on combination methotrexate and cyclosporine therapy, are at doses of methotrexate of 20 or 25 mg/week, which represents the dosage creep of methotrexate.

I think the requirement which we follow for monitoring on a monthly basis, once patients are on a stable dose of

Neoral now, is greater than what we would normally do for monitoring of higher doses of methotrexate anyway, which would be anywhere from six to eight weeks.

I haven't seen, it's an anecdotal clinical experience, a greater incidence of toxicity at that dosage level in combination than I would expect to see just with methotrexate alone at that level.

DR. PETRI: Dr. Lovell, I am not sure we have had a full answer to your question about whether it was necessary to monitor other laboratory tests including uric acid. If we could ask Dr. Torley to address the second part of his question.

DR. TORLEY: In terms of the clinical data that recommendation was based on we looked at -- I presented the data to you on the clinical notable abnormalities. There are patients, occasional patients who do develop uric acid levels that are high or magnesium levels that are low, although the incidence is low, and it is really based on the fact that individual patients have rarely developed these that we recommended, again on the conservative side, that these things be monitored for, because they are known effects of cyclosporine therapy.

DR. YOCUM: I would say that over the past 13 years of using this drug, while we have seen the trends that Dr.

Torley has talked about, I have never treated a gouty patient, nor have I treated a magnesium, unlike what we have seen in the transilient patients with higher dosages where I have treated gout patients, for some reason, whatever. It may again be the renal issue with uric acid that we don't see that problem, but I have never, ever treated a patient.

DR. PETRI: Dr. Whelton.

DR. WHELTON: Just as a sequitur on the magnesium issue, in fact, there is little in the way of pressing information in the literature that would say you need to monitor it with the exception of one study that we published some years ago, defining the added risk for aminoglycoside and nephrotoxicity in those who have subtle hypomagnesemia, but I think, listening to what I am hearing, it may be above and beyond what is needed at the dosing recommendations you were talking about.

DR. PETRI: Dr. Simon.

DR. SIMON: I was wondering if you could educate me a little bit more about the biology of methotrexate metabolism, because what you didn't do, and I thought was important, is that there is a very sensitive way to determine about the effect of methotrexate, which would be what happens to the size of the red blood cell.

You showed no data about that, and if there was a

subtlety in the way methotrexate was then altered in its excretion, then, perhaps that would be a way to determine that, and I thought there was also something about methotrexate in the cell as opposed to what you can then measure in the serum, and that some of that effect could be delayed and you would be unable to measure that, and perhaps the MCV somewhat did reflect that, so that in a six-month period, if you walked around with an MCV of 107, you might actually not show a fall in hematocrit, but in the second six months, you might show some significant biologic effects.

Could you comment on that?

DR. TORLEY: I am afraid I am not a methotrexate expert, but we have Dr. Kremer with us, who will be able to answer that question.

DR. KREMER: Lee raises some interesting points. There is no data which are really firm, defensible data showing that an MCV really predicts anything in terms of methotrexate metabolism, efficacy, or toxicity, although that has been controversial.

An earlier report suggested that there was an association with toxicity. That really has not been borne out in several subsequent studies. The intracellular methotrexate, products of polyglutamates are of interest to

methotrexate mavens. There is very little data, in fact, there is virtually none correlating methotrexate polyglutamate levels with either efficacy or toxicity, and I think it is one of the things that can be done in this area at this point.

DR. PETRI: I am going to ask that we move on to do the clinical perspective before our break.

DR. TORLEY: I have one more quick one, I am afraid. This is a quick one that you have probably heard.

DR. PETRI: Go ahead, Dr. Torley.

[Slide.]

To conclude, our dosing recommendations for Neoral is Neoral is initiated at a dose of 2.5 mg/kg/week. After four to eight weeks, if insufficient clinical benefit is seen and tolerability is good, the dose be increased by 0.5 to 0.75 mg/kg/day at four-week intervals.

The dose should never exceed 4 mg/kg/day, and the dose should be decreased by 25 to 50 percent decrements to control any increase in serum creatinine above 30 percent above baseline, and if the dose reductions do not control the increased serum creatinines, Neoral should be discontinued.

[Slide.]

Now, we arrived at the 2.5 to 4.0 mg/kg dosing range

based on this data that I showed you already, showing that starting at 1.5 mg/kg/day and holding the dose for eight weeks and then looking for clinical response, we did not over a reasonable amount of time, 16 weeks, see a clinically significant number of responders, indicating that the time to onset and this dose is not an effective starting dose. Therefore, we are recommending the 2.5 mg starting dose on the basis of this information.

[Slide.]

The top ceiling dose of 4 mg/kg/day has been arrived at based on two bits of information. This charts the cumulative incidence of ACR response rate against the maximum dose of cyclosporine prior to the event.

We can see that the majority of patients do achieve a clinical benefit by 4 mg/kg with very few patients actually requiring to go to doses of greater than 4 mg/kg/day, but the predominant reason for the 4 mg/kg ceiling is based on again safety, safety being the biggest concern here, and this slide illustrates the percentage of patients who develop a more than 50 percent increase in their serum creatinine by the maximum daily cyclosporine dose prior to event.

We can see that below a dose of 4 mg/kg, there appears to be a steady, gradual slope in terms of the incidence of

patients developing that more than 50 percent increase. As soon as you go to more than 4, the slope of the curve appears to increase, suggesting an increased risk in these patients.

So, again, to be on the conservative side and to maintain patient safety, based on the efficacy and this creatinine data, we are recommending a 4 mg/kg ceiling dose.

[Slide.]

In terms of the dose range that we would consider for use for the combination, the study started patients at 2.5 mg/kg/day, and we have no data at lower doses than this for a starting dose. If we look at the percentage of patients who respond, by 4 mg/kg/day, we can again see that the majority of the responses do occur in this range, but again, there are patients who do respond to higher doses than this, but again, to get the balance between the efficacy and safety, we would recommend, based on the creatinine data I showed you, that the 4 mg/kg ceiling dose be utilized.

Thank you. Will I turn it over to Dr. Tugwell now?

DR. PETRI: Yes.

Clinical Perspective

DR. TUGWELL: Thanks very much.

[Slide.]

My name is Peter Tugwell. I come from the University

of Ottawa in Canada.

[Slide.]

I would like to share with you the clinical perspective. I would like to point out that some of my recommendations may not match exactly that which you have in your briefing book, but reflect clinical experience and the way in which we do it in a real day-to-day practice.

[Slide.]

I would like to make a statement in terms of conflict issues. Our group has received grants in aid for the cyclosporine studies that you have heard described today, 2008, 654, and some other smaller studies. I have been a consultant on a number of protocols around cyclosporine development.

I have been a speaker at a number of conferences, and am a consultant in the preparation of this FDA submission.

[Slide.]

However, the view that I am going to represent now is not that of the company. It is just my view based on the following experience, first, as a clinical rheumatologist who has used cyclosporine for 15 years; secondly, as coprincipal investigator on two of the labeling studies that you have in your folder - 2008, coprincipal investigator with Dr. Bombardier, and 654, coprincipal investigator with

Drs. Pincus and Yocum; and thirdly, as cochairman of three international consensus guideline conferences on the use of cyclosporine in rheumatoid arthritis, cochaired with Professor Gabriel Panayi.

[Slide.]

This resulted in a series of publications which you may have seen in the British Journal of Rheumatology. This is the 1994 version. The 1997 version is in press, and this 1997 version included the microemulsion recommendations, the previous ones related primarily to the previous formulation.

[Slide.]

I would like to comment, to make three points and keep my comments brief, relating to the benefit/risk ratio to focus on firstly efficacy and tolerability as it relates to SAARDs monotherapy; and then thirdly to just address my summary view of what is going on with combination.

[Slide.]

This metaanalysis was presented by David Felson at the American College of Rheumatology meetings last year, describes a metaanalysis on the short-term data, and we have carried out several metaanalysis coming up with the same results, showing that cyclosporine is indeed efficacious and of a moderate level of efficacy.

In this particular metaanalysis, I should point out

that this is a conservative metaanalysis, though two presented by Dr. Felson would be done the same, because this includes not only tender joint counts, swollen joint counts, grip strength, but also includes sedimentation rate, which everyone accepts does not change with cyclosporine, although the CRP does.

I felt it appropriate to present the conservative metaanalysis at this presentation today by showing that it does have efficacy that is not different from the other second-line agents that we use with the possible exception of methotrexate.

[Slide.]

Secondly, I would like to comment on the tolerability, which I believe is very similar to the other slow-acting agents. Again, this is reflected in the metaanalysis that we carried out, published in the British Journal of Rheumatology, again showing the discontinuation rate due to toxicity is very similar to that seen in the other trials of the other agents that we use in these types of patients with aggressive rheumatoid arthritis.

[Slide.]

Thirdly, I would like to just make a comment in terms of the combination with other SAARDs. From our 654 that has been presented today, we certainly feel comfortable that it

can indeed be used with methotrexate. We had some previous open study experience. We continue to use this extremely widely in individuals with rheumatoid who have not gotten an adequate response to methotrexate.

We used doses of 20 and 25 mg -- commenting on the other comments earlier this morning -- without any problems at all, and we certainly currently feel that it's a partial response to methotrexate, for those clinicians that feel comfortable certainly should feel quite comfortable about going up to 20 or 25 mg, although the labeling officially is 20, as I understand it, in this country.

There is also some interesting data coming out. It's on combination with other agents. Our feeling was that people are going to use it in combination anyway with this current enthusiasm for it, so we had better get some experience, and so we have gone ahead and used it with a wide variety of other agents without any problems.

We have published with the open studies with gold, showing that again we get some very similar technical impression although they were open studies with gold, and there are some interesting studies which are now controlled coming out of Holland with chloroquine, again showing an incremental benefit in patients to whom you add another agent in patients who only partially respond to

methotrexate.

[Slide.]

So, how do we actually cyclosporine in day-to-day practice with patients with rheumatoid? Firstly, patient education. This is important. This is a slightly different drug than the drug that most of use, most rheumatologists and internists use.

It is really very, very important in our opinion to ensure the patients understands the importance of compliance with monitoring, and also the whole issue of the interactions, which I know is of concern to the committee from the questions already this morning and to avoid new medications without discussion with the physician. We have cards that we give to the patients, for example, and for the conditions we are using it.

Start cyclosporine at 2 mg/kg/day. We believe that you should give a split dose bid. We get asked about that, but that is the way the trials were done, and that is the way I believe you should do it, because that is the way our experience has been. I am sure that some people are going to want to argue for once a day, and again, some people have experience with that, suggesting it is no different, but our recommendation is to use the bid dosing.

We do believe that to get the effect and to allow these

patients to benefit, you need to increase the dose to 3 mg/kg/day at four weeks, and then 3.5 mg/kg/day at eight weeks in the absence of the adverse events, particularly the hypertension and the creatinine.

We follow the algorithm which is getting wide press now in terms of decreasing the dosage by 25 percent if the patient's serum creatinine is 30 percent or greater from baseline. The initial studies, we were using 50 percent as you have heard about today. We have now moved to the 30 percent. That leaves an additional degree of protection.

We do believe that you should evaluate the patient at two-week intervals until the maintenance dose is achieved and once the maintenance dose is achieved and you have got a steady state, then, we believe you should continue monthly until we get a lot more experience as long as the patient takes it.

I personally do not believe that you should decrease the frequency. Although our nephrology colleagues suggest that maybe we are being overcautious, I would like to recommend that we continue doing that, and that is in the international guidelines.

So, for as long as they take it, it is very important that they continue monthly and also have the blood pressure checked, as well as the creatinine.

We do believe it is important to have extra monitoring on patients -- although they certainly can benefit from the drug -- those patients who are 65 years of age and older, those with preexisting hypertension, and those using concomitant nephrotoxic agents or drugs that could indeed raise cyclosporine levels.

[Slide.]

So, in summary, cyclosporine is not the magic or silver bullet that will introduce remission in these patients. It is, however, a SAARD with efficacy that provides relief and clinically important benefit over placebo either as monotherapy of SAARDs or as SAARD combination therapy with methotrexate in patients with inadequate responses to methotrexate.

Experience in developing these guidelines internationally was benefitted enormously by the fact that it is approved in over a dozen countries, that there is a substantial experience worldwide. We have already got the previous experience from its use in many other diseases, which is a big advantage we are not starting with a new drug.

Having said that, I do believe the risks need to be taken very seriously by the rheumatologic community, and if they are, it is my personal believe that they can indeed be

managed by adherence to these guidelines which I am delighted to see will be reflected in the package insert.

So, finally, my own experience is cyclosporine is a useful product for the treatment of patients with severe rheumatoid arthritis.

I would be delighted to answer questions now or later.

DR. PETRI: Thank you. Are there any questions from the panel for Dr. Tugwell? Yes, Dr. Lovell.

DR. LOVELL: Two comments. Peter, would you talk about what difference it would make in your relative efficacy with other SAARDs if you eliminate the sed rate from your concerted analysis; and, two, is it your suggested dose increase rate somewhat more quick and aggressive than that recommended in the package labeling, and given the fact that a significant number of these patients don't respond until they have been on the drug for 12 to 16 weeks, why do you increase it so quickly?

DR. TUGWELL: The first question, as I understand it, was if you took out the sedimentation rates and looked at the end points that you believe will move, that bar increases up to the same level as the others. Again, I think we are talking about a drug that is very similar to sulfasalazine and gold in that metaanalysis.

[Slide.]

Again, I think it is important to point out that the metaanalysis has a whole variety of issues that you don't want to draw too much from this, because these patients in these various studies were not equivalent, some were early, some were late, and there is a whole variety of other issues, so I think this is a ballpark overall summary rather than getting down to the specifics of each bar.

DR. LOVELL: But at least you got out of the tar pit of equal efficacy to auranofin by doing this.

DR. TUGWELL: If that is your point, I strongly support it. I believe it is stronger than auranofin.

The second question was the aggressiveness of the increase in the titration of the dose, if I understood it. Again, I think it is similar to the methotrexate in that one would start, would go slow with the conservative approach, the same with the penicillamines of Jaffee approach that was used there, and that was our experience when we first started using cyclosporine, that the initial experience was 10 mg/kg and the 5 mg/kg meant that it was fine in experts' hands, but in terms of using it in the community, we felt that it was probably more important to start with a suboptimal dose and build up, so that one could get the patient educated as you move to the doses which were likely to be effective.

It is my belief that if you leave them on 2.5 mg/kg and wait, you are going to wait a long time, because as you pointed out earlier this morning, often you don't see it between 16 and 24 weeks any effect, and patients do not like that. You have great trouble with a tremendous amount of TLC, tender loving care, keeping those patients on the drug.

So, it is my sense this is a conservative approach. I do not believe the majority of patients will respond at that dosage, and therefore I want to get to the dose that will show a response, which is probably between 2.9 and 3.4.

DR. PETRI: Felix.

DR. FERNANDEZ-MADRID: You evaluate your patients every two weeks for creatinine and blood pressure?

DR. TUGWELL: Only while stabilizing the dose. Thereafter, monthly.

DR. FERNANDEZ-MADRID: And you say you advocate extra monitoring for patients over 65?

DR. TUGWELL: Correct.

DR. FERNANDEZ-MADRID: What do you do?

DR. TUGWELL: Again, we just want to be sure that they are stable, and so we would follow them two weeks for a period of 12 weeks, and then we go to monthly just to be sure. That longer period of time allows us to check to see that nothing is happening.

DR. PETRI: Dr. Luthra, did you have another comment?

DR. LUTHRA: Dr. Tugwell, you talked about a combination of methotrexate and cyclosporine and your experience. You also talked about some of the other drugs that you are using. Are the dosages of the other DMARDs that you are using in combination the prescribed recommended doses or higher doses that we end up doing in practice?

DR. TUGWELL: Yes.

DR. LUTHRA: That is one question. The other was do you have any experience of using multiple DMARDs along with cyclosporine at the same time, and have you seen any interactions under those circumstances?

DR. TUGWELL: Your first question, because of the way in which we practice clinically, we feel that we like to start these patients on methotrexate. We then go to the maximum dose that toxicity will allow, and the same with gold. Then, in those who have had a suboptimal response, we add cyclosporine without reducing the first drug.

So, our experience has been with using full dose of the other agents just because of the way in which you sequence it. There are some people who believe that you should less of each agent to reduce the toxicity, and that is one of the logics behind combination therapy.

It is our experience you don't get the sort of response

that the patient wants.

The second question relates to the addition of multiple agents. Hydroxychloroquine is standard in Canada before we start other agents in moderate disease. So, we have experience with hydroxychloroquine plus methotrexate plus cyclosporine, but it is limited to that, and they seem to do well.

DR. PETRI: Dr. Abramson.

DR. ABRAMSON: This is a follow-up question in a way. In moving this drug from protocol to broader use, what kind of restrictions were there in most of your protocols with regard to the numbers of slow-acting agents that patients had to fail before they were eligible for entry, and what is your view in the community about what kind of similar restrictions should be put on the use of cyclosporine in terms of the hierarchy of drugs?

DR. TUGWELL: Initially, as with all new drugs, one tends to start in patients who have failed a large number of other agents, so the original protocols had very heavy restrictions in terms of large numbers.

However, by the time it got to 654, because methotrexate was frequently the first drug that is started, that was the only drug to which they had been exposed before they were given the cyclosporine.

Again, our experience in a monotherapy trial is that as the study starts, the investigators tend to put on the late patients. As they feel more comfortable, they shift to the left. They give it to patients earlier and earlier, and again, the experience with the methotrexate suggests that I personally feel very comfortable in individuals who have only failed one DMARD, and that is the recommendation we make, and that is what the international guidelines say.

DR. ABRAMSON: Could that DMARD be hydroxychloroquine or should it be a drug like methotrexate?

DR. TUGWELL: Again, personally, I would like to see what methotrexate does before I would use cyclosporine, but there are some people who would go straight from hydroxychloroquine, and in Europe, I guess sulfasalazine is enthusiastically endorsed, so they would go straight from the sulfasalazine to cyclosporine.

DR. PETRI: Are there additional panel questions or comments? Yes.

MS. MALONE: My question is very similar to Dr. Luthra's. With taking methotrexate, you normally take it a certain period during the week. Would that administration change at all?

DR. TUGWELL: No. Again, initially, as you know, the recommendations were three doses at 12-hour intervals.

Increasingly, most of us use it once, the total dose all together, and we have suggested that people continue doing exactly what they were doing before they started the cyclosporine, and we haven't found a need to change that.

MS. MALONE: But, as you said, before you would start them on the cyclosporine, you would have the methotrexate up to the highest level.

DR. TUGWELL: Subject to the toxicity, because frequently they have problems with GI effects or mouth ulcers that preclude full dose up to 20 or 25.

MS. MALONE: So then if adverse effects occurred with the combination, would you say that it was because of the cyclosporine, the addition of that?

DR. TUGWELL: It depends upon what the adverse effect was. For example, if it is liver function tests, we would look at the methotrexate, but if it is the creatinine, we would look at the cyclosporine. We don't have a great difficulty in distinguishing between the two.

David, you wanted to comment?

DR. YOCUM: I have not seen any problem with the combination in most patients on methotrexate giving the usual daily dose of cyclosporine the same day that you take the methotrexate. The only patients that I have seen problems in are those patients who have been on

long-standing methotrexate, who have what I call the methotrexate sick syndrome, you know, the flu and headache for a day or two after. I have found in those patients that sometimes a co-administration of cyclosporine accentuates that sensation, and I have either had to lower the methotrexate dosage or sometimes we just hold the cyclosporine on that day.

DR. PETRI: Dr. Hochberg.

DR. HOCHBERG: Thank you. I would like to comment to Ms. Malone that in some patients who are partially responsive to methotrexate at the high doses, when cyclosporine is added, and they actually go into what we might call a drug-associated remission, that I have had the ability to reduce methotrexate dosages in some of those patients while maintaining them on a low but stable dose of cyclosporine. I don't know if Dr. Tugwell has such experience as well.

DR. TUGWELL: I have tended to keep it at the same level.

DR. PETRI: Dr. Pucino.

DR. PUCINO: Are creatinine changes different with the combination versus the single agent?

DR. TUGWELL: Again, we were looking for that particularly carefully, and the management is virtually

identical without, in fact, you wouldn't be able to tell the difference in terms of the way in which the cyclosporine is monitored.

Again, with monotherapy studies, we allow them up to a 50 percent increase in the creatinine. We have reduced that to the 30 percent since we moved to the combination, and one of the advantages of all of this is that we are probably getting away with a lower dose of cyclosporine, and it has certainly dropped from 3.4 to 2.9 on average in combination, so that there is a reduced exposure to the cyclosporine and the potential renal effects in the combination.

DR. PETRI: Dr. Simon.

DR. SIMON: Peter, given the increasing anecdotal reports of lymphoma associated with the use of methotrexate alone, is there any concern that you might have about the combination effect of cyclosporine or forms of cyclosporine with methotrexate?

DR. TUGWELL: Absolutely, and we have a consent form now for all the patients in which we give these agents, indicating that there may be an increased risk, but as Strom pointed out, as of now, the jury is out, we do not know.

DR. YOCUM: I might add to one of the earlier questions that of lowering the methotrexate, when we get the response that Dr. Hochberg suggested, we actually eliminate the

nonsteroidal. It allows easier use. I don't know, Peter, I think you have talked about that, as well, getting rid of what I consider to be the more concomitant nephrotoxic agent.

DR. TUGWELL: We find that we can move to Tylenol, which we like to do, and we actually have done a crossover study in patients crossing over between Tylenol and diclofenac, indocin, and sovendac, and again it is very difficult to predict which patients are going to do well and which patients are going to do badly, but it doesn't seem to be any big effect on efficacy or on the renal effects.

DR. PETRI: Last question. Dr. Lovell.

DR. LOVELL: The pharmaceutical database doesn't address the issue of the efficacy of cyclosporine as monotherapy in those patients who are methotrexate failures or methotrexate intolerant. What is the clinical experience of those who have greater usage? If you can't take methotrexate for any reason, how does cyclosporine work as a single therapy?

DR. TUGWELL: That was the majority of patients in our monotherapy study 2008. In fact, the majority of them had failed methotrexate, and there was no difference between those who had failed one drug versus those that failed three drugs.

DR. TORLEY: Peter, we have an analysis that looks at the ACR Responder rate, and the patients who failed methotrexate in 2008 versus those who didn't. With the patients who failed methotrexate shown in red, and the patients who didn't shown in green, and if we look at the completer analysis, which is most of the analysis I showed you, you can see that the responder rate in the patients who had previously failed methotrexate was 37 percent versus 8 percent in the placebo group, and then 30 percent in the patients never exposed versus 0 percent in the placebo group, this difference in the methotrexate failures being statistically significant.

DR. PETRI: Dr. Tugwell, thank you. We are going to take a 15-minute break now and then reconvene.

[Recess.]

DR. PETRI: Dr. Kent Johnson is giving the FDA presentation.

FDA Presentation - Medical

DR. JOHNSON: I am Kent Johnson. I am going to be making some sort of overview comments about the important issues that I think we have to discuss, and we may even have a little more time before 12 o'clock for further questions. I think we have got a good start on trying to get into the problems.

As you have heard from Helen and others, this NDA has a long history. I think I have been with it actually more than anybody at the company has, as a matter of fact. So I have been sort of sleeping with this drug for many years.

In some ways it makes me more confident I think than would be rheumatologists who are seeing all this data cold. There is a lot of data here. There is, as you know, all of what we call difference trials, all of the trials where the drug was shown to be superior either to another dose or to placebo have been done with the old formulation. Those are the trials 651, 652, 653, 2008, Peter Tugwell's early study, and then 654, which is the study done relatively more recently on background methotrexate in patients who are sort of partial methotrexate responders.

A number of years ago the company, because of the variable bioavailability and unpredictable absorption, worked up a different formulation. They came to us and asked how they could proceed with this, and we asked them for some pretty rigorous pharmacokinetic work to show parallelism here, and we also asked for another clinical study that compared the two formulations head to head, which is what trial 302 is.

All that information is now in, and we have got the database. Let me just make a few comments about each of the

individual trials. 651, as you recall, was the three-armed trial, methotrexate versus cyclosporine versus placebo. The whole scenario that we have already touched on is how this drug compares with methotrexate is kind of interesting.

651 was a relatively early study, and it was designed with a relatively conservative cyclosporine dose escalation pattern to it in the protocol, and it is possible that some of the inferiority of cyclosporine compared to methotrexate was attributable to that.

It is hard to conclude that that may account for the entire difference without doing another trial, but it would be interesting to actually see a head-to-head trial with methotrexate as currently used for both drugs, but we don't have that information.

Nonetheless, they are still worrisome efficacy suggestions with regards to cyclosporine even with this very go low, go slow regimen in 651, but the best efficacy data in terms of differences compared to placebo I think were offered by 2008, 652, the high dose of 652.

In addition, interestingly, if you look at trial 654, which was done presumably with pretty tough patients, there was a substantial cyclosporine effect over and above placebo when you added these onto the background therapy including methotrexate.

So, on the one hand, you have got trial 651 where the drug looks inferior to methotrexate, and on the other hand, you have got trial 654 where at least atop that subset of patients who are doing not too well with methotrexate, there is an additional benefit.

So, it is kind of an interesting contrast there. There is a long and interesting history to 653. We were at the time intrigued with the notion that possibly what are called concentration-controlled trials would be more powerful, it would be a more powerful way of demonstrating efficacy.

I think in theory that is true, but that was the spirit behind the attempt to design 653, and it wasn't gone into in detail because the results were pretty inconclusive, but the design, in brief, was an attempt to keep patients within predefined blood level windows.

Now, they started out at three different dose levels versus placebo, but the blood levels were monitored very closely, and the attempt was to jiggle the dose to keep the patients within that blood level window.

There also was enough clinical information by this time, and even earlier, that you couldn't ignore certain clinical effects that might occur, such as the bump in creatinine or other evidence of toxicity that may mandate a dose decrease.

So, right off the bat, this kind of maneuver was sort of strapped in a sense because you couldn't have that be the only device to alter your blood levels.

The upshot of the trial, which was I think four months or something like that, was that lots of patients were lost by the end of the trial, and I think the number of patients that succeeded in staying within their blood window that they were prescribed to stay within was a very small percent by the end of the trial.

So, you didn't have any patients left really at the end of the trial to draw conclusions.

Then, they did some PK studies, PK-equivalent studies which have been alluded to already, and probably don't need to be elaborated on. Then, they did trial 302. There was a question about formal equivalence testing of 302. I think, in general, 302, the point estimates trended a little better than Sandimmune, but they didn't do any formal equivalence testing.

Implicit in that kind of maneuver, you would have to decide ahead of time, you know, ideally, before you unblind the data, what small clinical difference you are willing to discard, you are willing to ignore and still come to the conclusion, if the test succeeded, that the two drugs were equivalent.

So, you really have to do a lot of negotiating ahead of time designing a protocol if you are serious about attaching a lot of validity to an equivalence test.

One big theme in the whole development, as has been alluded to, was the gradual acquisition of this dosing strategy that has been discussed this morning, and I think is really kind of a key dynamic in the whole NDA.

As we mentioned earlier, the very early trials used high doses, and, in fact, the one patient from the informal registry of rheumatoid renal biopsy patients of about 60 patients, the one patient who maintained a major creatinine insufficiency state was the one from one of the early NIH trials that was treated at 10 mg/kg.

But over time, especially in the early trials, as I had mentioned briefly this morning, trial 2008, which was designed in -- the protocol was signed off anyway in 1985 allowed creatinine increases by 75 percent.

So, there was this substantial ability to gather data to retrospectively analyze the effect of doses on creatinine insufficiency.

Could you put up the hand-drawn graph? Well, I will go over this one at the same time.

[Slide.]

We have two studies that give us useful information.

This one was already pointed out this morning by Helen, and it shows what happens to these curves when you exceed a 4-mg dose. In that case, you are already up to about 50 percent of your patients showing a creatinine increase, in this case, of at least 30 percent.

[Slide.]

There was a very steep curve when you looked at trial 2008 between the 4 and 5 mg/kg point. The 4-mg point would capture about 35 percent of your patients, and when you get up to the 5-mg point, you are up to about 60 or 65 percent of the patients. So, this was data that the company had, and that in the context of histologic data, I think in parallel, enabled them to work up these dose recommendations.

The histologic data has been alluded to also this morning. In terms of rheumatoids, there is very little density in terms of the data because we only have about 60 patients, and they are not systematically selected patients.

There was this New England Journal article that a number of people have mentioned that was about 180 patients who were about two-thirds adults and one-third children, I believe, the vast majority having diabetes, that did have enough depth to the data in order to enable them to do a multivariate analysis and determine which factors were the

strongest in predicting cyclosporine nephropathy.

I haven't talked to the authors, but in that study, one of them directly alluded to the fact that they didn't have enough blood level determinations in order to inject that component into the multivariate analysis.

So, we still don't have an answer as to whether or not over and above dose changes mandated by safety and dose changes mandated by efficacy, whether over and above that if you manipulated your dose according to the blood levels, that would also be beneficial.

I mean if you think about it, that would require a huge study to do, because you would need to look at subsets who have all those other items that can lead to a dose change fixed, and then within that subset, compare patients on a low blood level versus a high blood level. In any case, we don't have that information.

Now, what we do have is this 30 percent increase recommendation, which I think has been pointed out may be conservative. It makes this drug kind of interesting in a way because it is the only one in the armamentarium that has a clear marker for the upper limits of what you can use.

In general, I mean the reason methotrexate has crept up is because there hasn't been any sharp curve in LFT abnormalities, for instance, and the same is -- well,

auranofin at 9 mg, you run into a lot of diarrhea, but auranofin is not used very heavily these days.

But it is an interesting notion because in some ways we have got a better definition, I think, with this drug than some of the other second-line agents as to the maximally tolerated dose.

The other big dimension about the whole dosing strategy is reversibility. Helen showed most of this data. Unfortunately, when the company switched from Sandimmune to Neoral, they administratively curtailed a number of their follow-up studies that they were going to do subsequent to a number of the original Sandimmune studies.

The one exception, however, was the 2008 study, and that they did systematically follow up. Seventy-two patients were enrolled in the trial and 62 Sandimmune patients reached the end of six months, and at four months post-discontinuation of the drug, only 7 out of those 62 had a persistent creatinine rise above 30 percent.

Similarly, there was a subset of trial 302, which I think were just U.S. centers, who had their creatinine systematically followed up after discontinuation, and in that group, 3 out of 53 such patients, after three months off drug, still showed a creatinine increase of 30 percent.

So, there are a few exceptions, but in general, these

creatinine increases seem to be reversible.

Now, the issue of co-administration with methotrexate is a major one, and I hope we are going to have more discussion about this, this afternoon. There is a lot of different dimensions to this. As has been pointed out, they did do a formal PK interaction study which showed greater bioavailability by AUC measurement for the raw drug, but less by the 7-hydroxy metabolite, but the problem with all this is that we don't know the relevance of those two entities or perhaps something else in terms of predicting clinical efficacy with methotrexate in rheumatoid arthritis.

So, we sort of have to default back to the clinical database, which is 654 trial, and look at comparative ADR tables, and so on, which has been done. We are talking about 70-odd patients per arm, so it is not a big database, but it's not a trivial one either.

But we have to face the issue of how to describe the use of this medication in conjunction with concomitant methotrexate, and should the maximal dose methotrexate be lowered or should they be monitored more frequently, and so on, and so forth.

That is really part of a general attempt to describe the overall indication of this medication. I don't think anybody is using it currently as the first choice,

second-line agent, but it may not necessarily be the last choice, second-line agent either.

I worry, frankly, about patients who have failed a number of other DMARDs and get on this drug, and they are doing very well, and their creatinine bumps by 40 percent, and they don't want to stop the drug, and the physician may not want to stop it either, and we are not going to be able to tell them what happens.

Now, there are always unanswered questions about longer term utility, longer term risk/benefit of drugs. We can't require five-year controlled trials for approval. But this is one of the major longer term questions that could even be studied obviously.

Finally, this afternoon we are going to get into some of the other dimensions of labeling. The ACR Responder Index, which has pretty wide credence now, didn't 10 years ago or five years ago even. One of the approaches I think within the Agency is to try and make the labels more clinically user-friendly and helpful, and so on.

In the attempt to get away from the use of previous acronyms like DMARDs that we don't know really how to define, we are kind of being forced into a situation where we are probably going to have to describe clinical trials in a little more detail than we have in previous labels, you

know, the methotrexate or the auranofin label, for instance.

In that case, it might be nice to have a benchmark to compare across trials even though that is a very risky proposition to begin with. That is why we asked the company to do the ACR Responders, and you will see those in one of the proposed labels.

Finally, this afternoon, after 2 o'clock, we are going to, as a totally separate operation, we are going to talk about the pediatric issue light of the so-called Pediatric Rule, which is an attempt on the part of the Agency to enable labeling given sufficient PK and safety in diseases where it appears reasonable to extrapolate from adults down to kids.

I will stop there and we can open it up to further questions at this point.

DR. PETRI: Let me ask the sponsor first if they would like to reply to any of Dr. Johnson's comments. Let's open it up for a panel discussion. Dr. Liang.

DR. LIANG: I thought your comments were very helpful. Do you know what the history of the registry for cyclosporine use in the renal field, how did that originate? Was that a voluntary thing?

DR. JOHNSON: I have gathered that it's whenever people were biopsied for whatever reason, but I have never been

able to get a sense that there has been any systematic attempt to define eligibility for that, but maybe somebody can reply to that.

DR. FEUTREN: The kidney biopsy registry started in 1984, '83, '84, with the experience in patients with autoimmune disease at the NIH, and these patients were treated with very high dose, with patients receiving 20 mg/kg as mentioned in one of the slides. These patients developed increased creatinine. They were biopsied. It was at a time when also that chronic nephrotoxicity was being reported in heart transplantations.

It is how it started, but based on the awareness that cyclosporine could induce morphological changes which was not known before 1984. Bases on this awareness, people started to do routine biopsies, but the majority of these 192 patients were patients who had routine biopsies in particular in the trial in diabetic patients or in psoriasis patients. So at the very beginning, at the very high dose, we had about 20 patients who had biopsies with renal dysfunction whereas the majority of the others were routine biopsies.

DR. LIANG: This is not a registry in the sense that I was thinking about. It is just a group of patients that happened to have a biopsy at the NIH, who happened to have

toxicity. So there is no international effort to sort of track cyclosporine users through time? That is the sense I got from the discussion, but that is obviously wrong.

DR. FEUTREN: What we did is we proactively collected these biopsies, the data of biopsies from all trials, even, for instance, the rheumatoid arthritis trials, but it is extremely difficult to organize studies designed to look at biopsies because of the reluctance of clinicians to biopsy patients.

DR. LIANG: Whether we are talking about biopsies or other end points, there is none. Even if we call it that, it is not really a registry, or a post-marketing surveillance.

DR. JOHNSON: It's a collection. Where did the 60 rheumatoid patients come from in general though?

DR. FEUTREN: These patients came from a few studies in whom there were biopsies. Most of them were small studies. Some centers, other studies that had an addition to the basic protocol in which they conducted routine biopsies.

DR. JOHNSON: But just spot biopsies to kind of survey what is going on, not as a part of some formal hypothesis in any of these trials, do you know?

DR. FEUTREN: It was not based on statistical, it was a more descriptive endeavor looking at what happens to the

kidney morphology.

DR. PETRI: May I follow up on that? I think the advisory committee in general is very interested in what the plans are for post-marketing surveillance because we have brought up so many unanswered questions this morning.

If I could ask Dr. Johnson, have there been informal discussions already with the sponsor, and I would like to ask the sponsor to respond directly, as well, about what their concerns or plans would be for post-marketing surveillance.

DR. JOHNSON: Well, we have had discussions that follow a full gamut, the total gamut, and we haven't made any decisions for a lot of reasons, one of which we wanted to get input from you people. We want to get input from the committee about what they think might be recommended.

DR. LIANG: Can we do that legally?

DR. CHAMBERS: Can we do it legally? Yes. Is it something that is likely to be doable, probably not. Is it something that we need to contribute to the information we need about the drug? Not necessarily.

DR. PETRI: Let me just mention that I think this afternoon, as part of Question 1, the committee will be giving their recommendations about the areas we think are most necessary for post-marketing surveillance, but I

wondered if there were already plans underway.

DR. JOHNSON: Nothing that has been formalized. Let me put on one other slide, because it actually addresses the renal -- I am sorry, go ahead.

DR. APPEL: There are a small series of patients who have been biopsied serially with rheumatoid arthritis on cyclosporine compared to rheumatoid arthritis patients who have been biopsied who are not taking cyclosporine compared to controls, which are usually the transplant donors in one-hour biopsies, which have shown increased interstitial fibrosis. Unfortunately, the RA patients have more glomerulosclerosis even if they don't take cyclosporine, so it is not compared to the normal controls. Perhaps that is due to whatever other drugs we are giving them.

The other thing is the sampling error is tremendous in terms of these, because individual patients, if they have serial biopsies, sometimes the interstitial fibrosis actually goes down from the first to the second biopsy, or the second to the third biopsy. Well, that has to be sampling error. You can't get irreversible change going down. So, that is a difficult area.

The other thing I would say is that in the studies I have done, which almost all of the studies I have done with lupus have been collaboratively with the rheumatologists at

Columbia Presbyterian, one of the most difficult things is to try to log in biopsies at a set point, that if the patients are doing well, people are very reluctant to say do a kidney biopsy on somebody who is doing better, unless it is on a protocol with an experimental drug.

This is a drug which has been out and pretty extensively used, so I don't think most rheumatologists would take their patients who are doing well and biopsy them, and that skews things because the people who do badly get biopsied.

DR. JOHNSON: Let me make one other comment. Especially when the 653 trial failed, you know, this notion of a concentration control trial was very attractive, but it didn't work, it failed, and one of the rationalizations for this failure would be simply that the blood level is just too far distant from what is going on within the synovium if that is the site of action.

[Slide.]

So, I had the notion that maybe the kidney effect and the synovial effect are parallel pharmacodynamic assays here essentially, so I actually had the company a number of years ago try to investigate this possibility, in other words, that there is a correlation between how badly you can injure the kidney, as measured by some kind of summed change in

creatinine over the whole trial, and how well the joints do.

So, I had them do these dot-plot correlations, and if you raise that up a little bit, this is from trial 2008 which, as you recall, is the one that allowed the most flexibility in terms of creatinine, and if you AUC your full change in creatinine over the whole trial, that is what the horizontal axis is, and you just dot-plot it with the change in the number of tender joints, just selecting one parameter, that is what you get. That is a relatively weak association, so it didn't work, in other words.

I was hoping to find a pharmacodynamic assay here.

DR. LIANG: What about IL-1?

DR. JOHNSON: It wasn't measured.

DR. LIANG: I mean IL-2. Has anyone done a sort of functional assay comparing MTX with cyclosporine in terms of IL-2?

DR. TORLEY: No, we have not.

DR. JOHNSON: It's an idea, though.

DR. LOVELL: One of the things that came out of one of the protocols was that 75 to 80 percent of the participants in the study had protocol violations, and I think when you are trying to fine-tune serum levels of a bid medication, in a trial in which the majority of patients have protocol violations -- and I don't know which protocol it was -- but

I would think it would be probably generalizable in other protocols, is that you are probably damned before you get out of the starting block with those kinds of trough concentration type studies if 80 percent of your patients are going to have protocol violations.

DR. JOHNSON: Well, they were protocol violations because they were not able to be kept within that window. I mean the windows were too narrow, I guess, is one way to interpret what happened. They didn't enter as a protocol violation, they were at the end of the study deemed to be a protocol violation because they couldn't keep their blood levels within these narrow windows.

DR. LOVELL: But I think compliance is also another issue that you need to address if you are going to try to fine-tune these serum levels as an indicator.

DR. JOHNSON: Theoretically, you can bypass compliance if you are doing a study like this, and that would be its value. You bypass compliance and variable absorption, and everything else. I mean you skip all that, and you start with the blood levels.

I mean these trials have succeeded in, you know, for seizure drugs and things like that, but it didn't work here. It may have worked had the windows been larger and we could have kept the patients in there or it may still have failed,

I don't know the answer to that.

DR. YOCUM: I think you are hampered in these studies by the narrow window and trough that you have because the immunosuppressive concentration, which you looked 20 years ago at preliminary work with cyclosporine in the test tube, it was around 100 to 200 ng/ml. That was a nice consistent suppressive level for mitogen stimulation that way.

We know that if you go above 300 ng/ml, that is highly associated with significant rises in serum creatinine, and now you are given a drug, having been associated with 653, and I think Dr. Lovell is correct, you are trying to monitor people's dietary changes and everything else with a very difficult drug, and that was in Sandimmune times, too, it wasn't Neoral, which gave us more consistent, so I think all your comments are very correct. I think it would be very difficult just because of that very narrow window that you have.

DR. PETRI: I would like to bring up one thing that I think slipped through our safety discussion. We didn't mention lipids, and there is a large literature on accelerated atherosclerosis in cardiac transplant recipients who are receiving cyclosporine. Cardiovascular problems are the major cause of death in rheumatoid arthritis.

Dr. Torley, can you address this?

DR. TORLEY: We examined the percent of patients who developed total cholesterol levels more than 200 mg/dl, and we didn't have any of the LDL levels or anything. In terms of the incidence, the Sandimmune group had an incidence of 42 percent of patients who developed total cholesterol levels greater than 200 versus 34 percent in the placebo group, suggesting there was a slightly higher incidence in the Sandimmune-treated patients.

In terms of mean serum cholesterol levels across the groups, there was a greater rise in the Sandimmune-treated group than in the placebo group.

DR. PETRI: Dr. Torley, do you think this should be part of the labeling?

DR. TORLEY: Yes, I believe it is mentioned in the transplant group, but I certainly think yes. Actually, it is in our proposed label at the moment in terms of the number of patients with clinically notable elevations greater than 350 ng/ml at this time. It could be modified for a lower level.

DR. PETRI: Let me ask the panel if there are other issues that they would like to complete from this morning. Yes, Dr. Tilley.

DR. TILLEY: I just wanted to be sure I understood correctly. Dr. Johnson, your feeling, then, is that based

on the pharmacology and the strength of that evidence, and the fact that 302 did not show evidence to the contrary, that the two drugs, SIM and Neoral, are similar. Is that a correct interpretation of what you said?

What I was hearing you say that there was no formal test required of equivalency in this particular drug application, although you did have them do 302.

DR. JOHNSON: That's right. The problem is we would have to decide ahead of time what window we would allow, which we could do, and it is possible. I don't know what the odds would be, but even if you trend better by a point estimate, you still could -- I mean could you be statistically inferior -- you probably couldn't be statistically inferior, but you may still miss some kind of tight equivalence test that we might put forth.

That doesn't totally answer your question, but the other aspect of it is the pharmacokinetics are what help link this whole thing together.

DR. TILLEY: But my question to you then is you feel that that in itself was sufficiently strong information?

DR. JOHNSON: The pharmacokinetics, yes, they were strong. I think they were sufficiently strong, and I think they are probably the key link in the whole thing. I mean because if they were weak, you know, we would be in trouble.

But I think the strength of that link allows us to attach credence to all of those earlier trials.

DR. HAUPTMAN: If I may, I might be able to address this equivalence issue somewhat. Although we didn't formally plan to look at it that way, we do from 302, you will recall there are four main variables and two global scores, one of which to patients is already significant, significantly better for Neoral than for Sandimmune, and the two swollen joint counts.

Now, we do have confidence intervals on the difference in the change in swollen joint counts at end point -- of the two joint counts. For swollen joint count, it ranges from minus 1.89 to 1.95 joints. The minus side, SIM is better, the plus side Neoral is better. So that is just about symmetric, about zero.

For tender joint counts, it ranges from minus 0.81 to 5.61. So, for that, the confidence interval is decidedly shifted towards the Neoral is better part of the spectrum, and that is the results we have for 24 weeks, and I think what you see up here is the results out at 52 weeks, not in terms of confidence intervals, but the p values.

DR. TILLEY: Who is in those analyses, everybody, or just the people who got out to those points?

DR. TORLEY: This was based on an intent to treat

analysis.

DR. TILLEY: Doing what with the people that you didn't have follow-up on?

DR. HAUPTMAN: It is less observation carried forward, and that was what the confidence intervals that I gave you for 24 weeks. If I actually give you the confidence intervals for those people who made it out to 24 weeks, are actually more favorable for Neoral, but I didn't give you those because they are biased by just looking at completers.

DR. CHAMBERS: The way the Agency has treated this for this application is basically the same, because their bioequivalence data supports it, and the one clinical trial did not show a gross deviation, and we have only used that trial as a gross deviation just in case the actual cyclosporine level was far misleading.

DR. TILLEY: That is the way I was interpreting what had been said. Thank you.

DR. PETRI: Additional questions?

DR. APPEL: If this is relevant to the point in terms of comparisons between Neoral and Sandimmune, that almost virtually all of our patients on transplantation now are getting Neoral just because of better absorption, and this has been trend across the country. So, I think that probably half of all the transplant patients in the country

now are getting Neoral, in fact, in all new ones in most centers are being started on this, again just because of more consistent absorption.

DR. PETRI: Dr. Whelton.

DR. WHELTON: I wanted to ask Dr. Torley if you could possibly put your hand on -- and you have been so impressive at taking out the slides instantaneously -- it is the one where you show the break point between 4 to 5 mg/kg correlated with increase in serum creatinine as identified as percentage over baseline. I can't seem to find it here.

DR. JOHNSON: 302?

DR. WHELTON: I don't know. I thought that that was a composite graph.

DR. JOHNSON: He is interested in the increase in creatinine as a function of the dose. You have a composite graph, I think.

DR. WHELTON: And you put in two exponential curves, and they break right around 4 mg. Wouldn't it be more correct -- and I defer to the pharmacokineticists on the panel -- to actually convert the ordinate into a natural log, and I am sure that line would just straighten out, and that what we would see is that with increase in milligram dosing, there is a progressive increase in toxicity, that there really isn't a true biological break point between 4

to 4.25, correct? Thank you.

I think that may be a more correct way to present that and that we are actually seeing a continuum, and so I wouldn't get hung up on the figure of 4 mg and say if you go above that, there is something very unusual and toxicity suddenly takes off. It is the way the data are displayed. I believe that would be a reasonable way of replotting the data.

DR. PETRI: I wanted to ask that we adjourn at this point for lunch, reconvene promptly at 1:00 p.m. for discussion questions.

[Whereupon, at 12:01 p.m., the proceedings were recessed, to be resumed at 1:00 p.m.]

AFTERNOON SESSION

[1:05 p.m.]

DR. PETRI: We will start this afternoon by addressing the questions given to us by the Agency.

Discussion and Questions 1 and 2

I am going to ask that we actually divide Question No. 1 into two parts. The first will be a discussion by our panel about efficacy, and the second part will be the discussion of the acceptable risk/benefit ratio.

I would like the second part of the discussion to be very specific and to address the labeling, but let's start first with the issue of efficacy. In fact, I would like to go around the panel, perhaps starting on this end, and if you don't have a comment, you need not make one, but if you wish to make a comment about efficacy, please do.

DR. LOVELL: I would like to ask the sponsor to put up a slide. I was going to do that before lunch. Is it possible to do that now?

DR. PETRI: Yes, whenever the panel would be helped by additional information from the sponsor, please ask for it.

DR. PETRI: Dr. Whelton.

DR. WHELTON: On efficacy, no.

DR. PETRI: Are there questions or comments about efficacy?

DR. FELSON: You want comments? I have no questions.

DR. PETRI: Dr. Tilley?

DR. TILLEY: No questions.

DR. SIMON: I have no questions about efficacy.

DR. PETRI: Dr. Abramson?

DR. ABRAMSON: No, I don't have a question about efficacy.

DR. FERNANDEZ-MADRID: I have no question, but I have a couple of comments. I think it has been shown that it is an effective drug. I think all the trials have shown that it is effective. However, the indication for concomitant use, I don't know if this is included in the question or not.

DR. PETRI: I am going to ask you to wait until we get to Question No. 2, which is really on indications.

DR. FERNANDEZ-MADRID: All right. Then, I will defer it.

DR. PETRI: Dr. Liang?

DR. LIANG: No questions.

DR. PETRI: Dr. Luthra?

DR. LUTHRA: No.

DR. PETRI: Ms. Malone?

MS. MALONE: No.

DR. PETRI: Dr. Pucino?

DR. PUCINO: No.

DR. PETRI: Dr. Lovell?

DR. LOVELL: Dr. Torley, would you put up that slide again where you show the comparative efficacy of the various single drug studies? I think it is the result of metaanalysis, the one you pulled up before where you didn't include the sed rate.

DR. TORLEY: I am sorry, the one that did or did not include the sed rate?

DR. LOVELL: Did not.

DR. TORLEY: Did not.

[Slide.]

DR. LOVELL: If we would put error bars around those bars, where would it fall, do you know?

DR. TUGWELL: David, you were out of the room when we presented this. Can you respond since it is your data?

DR. FELSON: I am not sure exactly how you got this data, Peter.

DR. TUGWELL: It is taken directly from your abstract. I have the abstract in my hand if you would like to see it.

DR. FELSON: I stand corrected. I am not sure, Dan, what were you asking? You want standard error bars around these?

DR. LOVELL: Yes.

DR. FELSON: They are real wide. I mean they are real

wide to the point where if you want to know whether any of these drugs is significantly different from any other, the only ones that really are significantly different here are auranofin and all of the other drugs which aren't significantly different from one another, if that is the sort of question you are asking, using random effects appropriately adjusted for or attempted to be adjusted for a lot of the variability between trials.

DR. TUGWELL: The standard error was 0.13 for cyclosporine only, and overall effects, 0.41.

DR. FELSON: Right, and that is the standard error, I mean so there is a very wide estimate of efficacy here, comparative efficacy.

DR. LOVELL: Can anyone respond to the fact that in the trial given for review here, there was a significant difference between cyclosporine and methotrexate in that prospective trial, whereas, it is not shown here, why that might arise?

DR. TUGWELL: My response would be I think what Kent was pointing out in terms of the way in which the dosing was done with the cyclosporine was much less aggressive than in the studies that I was involved in.

DR. FELSON: I would add to other explanations, Dan. One is that trials aren't all the same, that there is a lot

of variability from trial to trial in terms of relative efficacy, and the other is that the way that that trial data were analyzed, using ACR response criteria, and having a direct comparison which doesn't force you to factor in a lot of the variability between trials, actually creates a bit more efficiency than the metaanalysis of multiple trials, so there may actually be more power to detect a difference between methotrexate and cyclosporine in one large trial than there might be in that kind of context.

DR. PETRI: Hearing no additional comments from our committee, I think that we are unanimous that there is efficacy for this drug.

May I see a show of hands for, yes, there is efficacy?

[Show of hands.]

DR. PETRI: Are there any who wish to vote nay?

[No response.]

DR. PETRI: I would like to address most of our discussion as far as the second part of this, and I would like to make that a safety discussion, focusing on the proposed labeling. I want to remind the committee members that we have the proposed label.

The last section says "Proposed label," and to help us focus, I would like you to turn to line 281 of that proposed label, where the first line that is underlined is

"autoimmune diseases/rheumatoid arthritis."

Just to refresh all of our memories about the morning discussion, there were many very specific comments and suggestions about the labeling, both in terms of renal complications, the issue of dosing, interval increases, the issue of basal cell carcinomas and cervical carcinomas, the issues of renal insufficiency, and the issues of obesity.

If I could now open this up for discussion, and for those of you that have comments, would you please address those to the appropriate section in the label.

Dr. Simon.

DR. SIMON: First, can I make the comment that before addressing each appropriate section in the label, that I am seriously concerned about the general use of a drug such as we are discussing in the particular climate of medical care that we exist within, and who would be using this drug, and how it would apply to individual patients once it was approved.

So, I would like to see us do several things in this discussion. I would think that given the concerns that we have regarding toxicity, that we would want to be clear in who should be able to use this drug for patients with rheumatoid arthritis. That is number one.

Number two, I am very concerned about being incredibly

clear about what needs to be followed up on, and that, in fact, it makes it so restrictive that certain care environments would shy away from putting it on their formulary because of the concerns regarding costs of follow-up and cost of drug.

The third thing relates somewhat to the things that you just related to the individual patients and their problems. There was this comment made before about, gee, they might not give this to someone with a creatinine of 2.2 or 2.3, and I would like us to debate the possibility of actually requiring a five-year patient database follow-up that the drug company would have to support and establish -- I am sorry -- the sponsor would have to support and establish to ensure that we truly understand the ultimate outcome of the use of this drug in patients over a significant period of time.

I don't think that that would necessarily require an invasive kidney biopsy, for example, but it would require very careful recordkeeping about intervention with the patient, blood pressure measurements, the medical record would have to be achieved at a certain level that we would have the data over time to assure that we really understood the implications of using this drug even in patients that have failed one or two DMARDs previously.

That is kind of like a general comment about this.

DR. PETRI: There is going to be an artificial separation of our discussion on safety, which is part of Question 1, and indications, which is part of Question 2, so we will address some of your concerns under No. 2. I think part of No. 2 is not just indications, but where is this going to occur, is it going to occur in any primary practice setting or is it going to occur in a rheumatology setting or nephrology setting.

In terms of post-marketing surveillance, I think we should discuss that once we have come to some sort of consensus about what are the labeling concerns, because the post-marketing surveillance, I think is going to be very dependent on the concerns that we, as a committee, want to address.

Perhaps we could start with concerns about the labeling in terms of the renal issues. Dr. Whelton, could I ask you, having read this section here under the labeling, whether there are additional things, could you specifically address what you think would be appropriate in terms of a renal insufficiency labeling here?

It is the last section. It is line 281 under "Proposed labeling."

DR. WHELTON: There are two labels here, that is the

problem.

DR. PETRI: Can you address us to the one that you wish us to look at?

DR. JOHNSON: The two labels are going to be numbered differently, though. That is the problem. If you open to the proposed label section, at least in my book, it is the first label. If you go to line 281, I think it is the beginning of the autoimmune --

DR. PETRI: It is page 2-13 is the one I am looking at. I just want to make sure that the Agency directs us to the correct proposed labeling.

[Audience comment.]

DR. PETRI: I am sorry. There are comments from the audience that we can't hear, if you could come to the microphone.

DR. LOVELL: Kent, I don't know what you mean by there are two labels here.

DR. JOHNSON: Maybe there is just one. In the lower righthand corner there should be 2-13, page number?

DR. PETRI: Yes.

DR. JOHNSON: That is the page everybody should be on.

DR. PETRI: There is a statement there about is renal dysfunction as a potential consequence of Neoral, and therefore, renal function must be monitored during therapy,

and then it goes on to talk about serum creatinine, elderly patients should be monitored.

DR. JOHNSON: Do you see that, Andy?

DR. WHELTON: Yes, I do, but all of that is entirely reasonable, but when we get into the issues of not necessarily minutia, but taking the elderly individual who has muscle mass loss, it goes right back to the discussion we had this morning, raises the issue of doing things be it iothalamate or technetium DTPA studies to be more precise in defining the renal function.

On balance, I think that that is expensive, and it's cumbersome, and when some of these more simpler guidelines are used with individualization of attention, this is probably more reasonable in the real world.

DR. PETRI: Let me ask for additional comments. Dr. Whelton, if I understand you, you would not want to add to this label as it stands in terms of renal toxicity and particular monitoring of subgroups?

The concern that we raised this morning was the subgroups with renal insufficiency and the issue of NSAIDs.

DR. JOHNSON: You don't get on the drug if you have renal insufficiency according to the label, correct?

DR. FELSON: But what is renal insufficiency?

DR. PETRI: I think we need to define it. Dr. Felson

has asked that we be more specific about defining blood pressure, as well.

DR. WHELTON: Kent, help me with the dosage and administration, because the label says, "See special monitoring." What line does that go back to?

DR. JOHNSON: Essentially, you escalate assuming you are not getting an effect and you stop at 4, or you stop at a creatinine over baseline of 30 percent. Isn't that right, Helen?

DR. TORLEY: Special monitoring is at page 2-30, towards the back.

DR. LOVELL: The information about specifics for dosages start halfway down on page 2-28.

DR. PETRI: Very practically, the only people who are going to read this label may be rheumatologists when they are starting to use this drug, and I think it is already obvious to the panel that it is hard to follow.

DR. LIANG: This is terrible. Are we going to wordsmith?

DR. PETRI: No, we are not. I think we want to give major messages exactly.

DR. LIANG: This is poorly written. This is too small. I would limit it all to immune diseases. This is specifically RA.

DR. PETRI: This is quite an interesting creep. Immune diseases are listed before rheumatoid arthritis here.

DR. LIANG: That is misleading.

DR. PETRI: I would like to ask the panel if there is a consensus that this should have much more detail in terms of a definition of renal insufficiency, actual wording about monitoring on NSAIDs, concern about the fact that we don't know what obesity is going to do in terms of toxicity.

DR. WHELTON: One of the issues that isn't at least as I flip from one page to another, and I read this a few days ago, and it didn't impact on me that there is a definition of what happens with renal function as a consequence of the aging process, so since this really is a key aspect to influence therapeutic decisions, it probably does need to be expanded, because the fact of the matter being that in an otherwise acceptably health individual who reaches age 80, 50 percent will have 50 percent reduction of glomerular filtration rate just based on age issues alone. So there are some of those aspects I think probably do need to be expanded upon.

DR. PETRI: Dr. Simon.

DR. SIMON: In extension of that, Andy, if you then take people who have rheumatoid arthritis for 20 years, and they have been on nonsteroidal inflammatory drugs for God

knows how long, that those patients are at significantly increased risk of having further nephropathy, and thus, it is really imperative for us to identify, as Dr. Petri has mentioned, that patients that have been long term either nonsteroidal anti-inflammatory drug use or acetaminophen use perhaps need to be thought differently about and monitored differently as a result, right?

DR. WHELTON: But if the proposal was as we heard to ask for at least two baseline serum creatinines, and if you compare that with the data that may be generated by something such as technetium DTPA study -- and I must say I have recently done such a trial to look at replicate values of DTPA clearance as a marker of GFR in those who have mild progression of renal impairment, and I was surprised in a standard lab by the enormous standard error on these repetitive analyses.

I know, Michelle, you have had great experience in that issue and published on such a concern in lupus patients.

DR. SIMON: But if the serum creatinine is 1.5 in that scenario, does that preclude the use as the baseline trial before therapy, would that preclude the use or change your dosage schedule, and should that be identified in the package insert? That is really what my question is.

DR. WHELTON: I don't think it would change your

therapeutic decision at all. It would establish a baseline for that individual patient, and so that would be I think the important issue of doing at least two baseline serum creatinines to get around this issue of the 30 percent variation just based on the assay methodology alone, to give you a little bit more credence when you do see an elevated creatinine as a follow-up.

It may well be that we would want to recommend doing at least another check on that elevation of creatinine before making a therapeutic decision.

DR. SIMON: Maybe I am confused. Is there some point that you would say that you would not give this drug, a serum creatinine would return that the mean would be some number, is there some point you would say above that they shouldn't get this drug?

DR. WHELTON: Based on the available data in the transplant literature, one would not say that. There will be many occasions where, with an elevated creatinine, you would want to continue the drug albeit it at a reduced dosage.

DR. FELSON: That is one of the concerns is the risk/benefit concern. It is do different than in transplant where you might lose the transplant.

DR. WHELTON: You have clearly got to tie that into the

decision.

DR. LOVELL: Lee, it seems to me that the patients that were studied on this drug, that we had to review in this document, had been on average with their arthritis for 10 years plus in all the studies, so that they were kind of not neophytes to NSAIDs, and that the approach taken by the company has been I think quite a conservative one to protect the patient against short-term renal toxicity.

The question I have is really in terms of long-term renal toxicity, five years, 10 years, because this drug appears to be like methotrexate, that if you get a patient who shows benefit, then, they are liable to be stuck on that drug for a long time, because the efficacy drops off quickly, and there may be patients, in fact, there probably will be patients given the way the indication is written, who will be on long-term therapy with methotrexate and cyclosporine together.

I think the company is taking a rather protective approach towards renal toxicity in the short term. The unknown for me -- and perhaps the registry would address the issue that you brought up -- would be the five-year outcome of patients who have been on this drug.

DR. PETRI: I am not sure that I have actually had a consensus of the committee about some of these renal

toxicity issues. Specifically, have we addressed whether this drug can be used in a patient with mild renal insufficiency?

DR. SIMON: Could you define that, please? What do you mean by "mild renal insufficiency"?

DR. PETRI: A glomerular infiltration rate that is about 50 percent of normal.

DR. WHELTON: Actually, I would redefine that, and I would say mild renal insufficiency is at a point in time where approximately 75 percent of original renal function is lost, because that then becomes the break point where you begin to see changes in hematocrit, you begin to see changes in calcium, phosphorus metabolism, you begin to see the subtle aspects of acid-base changes.

So, that usually in most adults will be circa creatinine of 3 as a rule of thumb. That is a break point, so I think I would say by definition, up to a serum creatinine of 3, taking the -- I note that the average age of the patients in these trials being in the 50s, age range of the 50s. That seems entirely reasonable, and I think that the risk/benefit ratio, that should determine the issue about giving the drug.

DR. PETRI: Dr. Felson.

DR. FELSON: Let me raise some concerns about that

threshold that you just mentioned, Andy. One is that it sounds like the company has never really tested this drug in people with creatinines that high, that the trials have been limited to people with essentially normal range creatinines, and I think it would be helpful at this point to know exactly what the acceptable upper limits of creatinine in these trials was, because I would be reluctant to suggest that it might be safe in people with creatinines above that level.

I think another important concern, one that was mentioned earlier was the muscle wasting that occurs in RA leading to perhaps inappropriately low creatinines. The other is the fact that these trials were done, if I remember right, the mean age of subjects in these trials was 50. The mean age of people with rheumatoid arthritis in the United States is more towards 60, and this is increasingly an older person's disease.

Creatinines may not as well reflect diminutions in renal function in older people, and I would be concerned about a relatively high level of creatinine, in fact, I would be concerned about a normal level of creatinine in an older person hiding a substantial amount of renal insufficiency, and I wonder if we ought to make a bar that is substantially low, so that we don't put older people at

risk of this drug, who, in fact, have a substantial amount of loss of nephrons.

So I am concerned about putting a creatinine at -- I would actually like a number here. I would like a number, so that practitioners who are likely to use this medicine can say, look, this is a creatinine or some measure of renal function above which we would be concerned or above which you should have great concern in using this drug.

I think we need to look to you to what the most thoughtful estimate of what a reasonable number is based on a lot of considerations, and obviously, the other consideration is one we have already mentioned, which is risk/benefit, this is not transplant, this is a situation where there are a lot of other drugs available, and I wouldn't want to put someone into renal insufficiency.

DR. WHELTON: Under those circumstances, we really need the inclusion of a nomogram that would convert serum creatinine to glomerular filtration rate with modification for sex, age, and weight. That way we could be much more clear-cut in the identification of mild renal insufficiency, and frankly, although the data are not there, I would say if we have to come up with a definition, it would be up to a serum creatinine of 3 or a GFR of 35 or less.

DR. APPEL: It is interesting, nephrologists think

alike because that is exactly what I would make a recommendation to put a formula, such as the Cockcroft Gault formula, which has been used many, many times, which uses age, weight, and the serum creatinine. It accounts for the fact that females may have less muscle mass than males multiplying by 0.85, and this will give you an estimate of the creatinine clearance, that based on the serum creatinine, so there is not the inaccuracies of measuring 24-hour urines or urine collections. At the same time, all the concerns of the panel in terms of a small, tiny elderly lady, who may have a very low glomerular filtration rate even though her serum creatinine is 2 1/2, you would be able to use some cutoff.

Now, whether the cutoff should be a GFR of 30 cc a minute or 40 cc a minute, I will leave this to be worked out, that those are difficult areas, but nevertheless, relating the creatinine to weight and at the same time to age is easy enough to do by the Cockcroft Gault formula because that has been worked out in many people, and it is used pretty standardly by many -- in fact, I think it is on package inserts if I am not mistaken.

DR. TORLEY: Dr. Felson, if I can just specifically address your question about what was used in the studies, we used the same central laboratory for the majority of

studies, and listed there is their normal range for serum creatinine, which was 0.8 to 1.5 mg/dl.

I believe we later on amended the studies to have a slightly lower level for females at 1.3 mg/dl, but men were allowed up to 1.5, and women to a maximum of 1.3 mg/dl to be eligible to enter the study based on presumed normal renal function.

DR. PETRI: Felix.

DR. FERNANDEZ-MADRID: With the definition that we have heard, my answer to your question would be no, but since we take care of these patients, I would be very worried about taking care of a patient with rheumatoid arthritis with a creatinine above 2, between 2 and 3. I would be very worried, particularly because we would treat these patients for years, not for 24 or 50 weeks, but for 100 weeks, 200 weeks, 300 weeks, and I think lower levels than have been mentioned would be a concern for me.

DR. PETRI: Dr. Simon, I think you were next.

DR. SIMON: Again, I wonder whether or not the people who have had a lot of experience with cyclosporine could actually help us with this, because we have not seen data presented to us about anybody that has been treated with creatinines above 2, and perhaps Dr. Yocum or somebody who has actually used this a lot, or Dr. Tugwell could comment

on really what happens under these circumstances.

DR. YOCUM: I have used the drug extensively. We did a follow-up abstract, I think it was last year, looking at about 36 of our patients over a three-year period, but again we used this same dosing guidelines, and I would not put a patient with a creatinine outside the upper limits of normal on this drug, because the only patient that we found after three years who still had an elevated serum creatinine above 20 percent was a woman with RA, older, hypertensive, whose was controlled during the trial, but she started with a creatinine of 1.5, which at the earlier studies, as Dr. Torley brought up, was allowed in the study, but she was the only patient that we saw persistent elevation even after she was off drug. I still follow her, and that persistent elevation stays there.

So, my recommendation when somebody calls me, and they have a creatinine outside the upper limits of normal, I say don't put them on this drug because in the general practice, why give yourself a headache.

DR. SIMON: I think that is a very useful comment for us when we are searching for a cut point, that one suggestion now is not to use this drug in anyone that has abnormal kidney function to any degree if it is outside of the normal range of serum creatinine.

DR. LOVELL: Sitting on this side of the table, I am listening to that side of the table, and you are in the unusual situation of kind of mentally trying to figure out a way to make the restrictions for this drug less restrictive than the sponsor is asking for with the exception I think that we are talking about serum creatinine being a poor surrogate marker for renal function in the elderly, and perhaps we ought to kind of expand the wording on age effect on renal function in the label or make it more restrictive in that group.

But what you guys are talking about in terms of allowing the creatinine up to 3 and 30 percent renal function is actually more liberal than the company is wanting to put in the label.

DR. WHELTON: Well, that was really approaching what is the definition of mild renal impairment. I mean the fact of the matter is no data are available to guide us as to therapeutically what will happen and side effectwise what will happen. What we are trying to come up with is an acceptable definition of mild renal failure across the board in all candidates from somebody who was 35 years old to somebody who is 85. That is part of the problem.

DR. PUCINO: One solution would be to say that we do not -- in the insert -- to say that we do not have data on

patients with creatinines greater than 2, and we don't know what the long-term effects are of that, and until that data is available, we do not have any official guidelines or something to that effect.

DR. PETRI: Let me ask Dr. Johnson, is that a reasonable thing to put in the labeling?

DR. JOHNSON: I think somewhere in the label there would be some kind of statement that mild renal insufficient patients haven't been studied. I mean what I would like to see is to have it studied, actually, and then we would know.

DR. PETRI: We are going to have our wish list at the end of this discussion.

DR. CHAMBERS: One of the other options to take is to set a relatively low level, and say that if you have a patient that has a creatinine above this, additional testing should be done to make sure that the creatinine is truly reflective of what the GFR is.

DR. PETRI: Does the committee feel comfortable with that kind of wording? Dr. Luthra.

DR. LUTHRA: Michelle, I don't think I am comfortable in saying anything beyond what the normal range is. That is all the data we have. That is really where we should leave our recommendations to. Speculating beyond that, I think it is reasonable to ask them to gather data, but I am not

comfortable in making statements of leaving some loose ends like that, the creatinine up to is appropriate under certain circumstances.

We have no data. Just leave it with the data that we have rather than speculating beyond that.

DR. PETRI: So the consensus I am hearing is that in the absence of data truly relevant to the rheumatoid arthritis population that the committee feels more comfortable that this drug not be given to RA patients with renal insufficiency. Is there dissension about that?

DR. SIMON: Will you define renal insufficiency?

DR. PETRI: No, we are not defining renal insufficiency.

DR. SIMON: So then I would turn that around and say we comfortable in giving this drug to people who have normal kidney function, and that that is the only patient population that we would be comfortable with.

DR. PETRI: Dr. McGuire, did you want to add to that?

DR. MCGUIRE: Yes. I became a little concerned when it sounded like we were setting standards that actually had not been observed in practice in terms of serum creatinine, and I don't see how we can do that. If the sponsor has taken the position that they would not treat if the creatinine were out of the normal range, then, I can't conceive that

the labeling could reflect anything other than that.

DR. PETRI: I think there is now a consensus that this drug should be limited to patients with normal renal function.

Dr. Felson, did you have another comment?

DR. FELSON: No. Michelle, were you thinking of a particular number when you said normal renal function, or did you want just that label? We have just had a long discussion about what normal renal function is, and I am not sure --

DR. PETRI: It is such a matter of technology. Normal renal function, if you have technetium DTPA at your bedside, it's one thing. If you are going to go by serum creatinine, it is something else, and I wonder if we shouldn't just leave it as normal renal function, but let me ask Dr. Whelton whether that is reasonable.

DR. WHELTON: That would be much safer because you can come up with then a definition of what is the normal range of glomerular filtration rate in a lady who is aged 85 and who weighs 85 pounds. One can come up with such a calculation and identify that the upper limits of that range would identify important renal impairment for a comparable 35-year-old who weighs 190 pounds.

So, I think it would be much safer to say, quotes,

"normal renal function."

DR. LOVELL: If I heard you correctly, you and the other nephrologists, that could be done with the serum creatinine with the appropriate formulas or graphs, that sort of thing. You wouldn't require additional laboratory tests beyond serum creatinine.

DR. WHELTON: That is part of the package insert in many of the aminoglycosides that are currently approved, so something very similar I believe would be exceedingly helpful.

DR. PETRI: Let me ask Dr. Felson, does this address your question that we would define normal renal function using the equation that Andy has suggested?

DR. FELSON: I guess it does, Michelle, except I am nervous about what I would characterize as the degree of creatinine clearance loss that he is talking about, the degree of GFR loss he is talking about, because that, in fact, is a much greater loss in renal function than any of the trials have used.

DR. WHELTON: No, I mean but you could have a serum creatinine of 1.4 in that theoretical 85-year-old lady who weighs 95 pounds. Her serum creatinine will appear to be quite reasonably acceptable. Her calculated glomerular filtration rate may be something like 37 ml per minute, but

yet for her, at her age, and her size and her sex, that is within the normal range for her.

DR. FELSON: Andy, that is not necessarily the example I would conjure up to try to get at the difference between our definitions. The example I would conjure up is the 30-year-old, perhaps on the large size man, whose creatinine is 1.7, okay, and whose calculated GFR may be down a little bit, and I guess I would wonder where he sits and whether you would give him this drug, or let's say his creatinine was 1.9, you know, something where I have been taught, I think in part by you, that I would be reluctant to use nonsteroidal drugs in this kind of person, and the reason I would be reluctant to use nonsteroidal drugs is almost for the exact same physiologic reasons I should be reluctant to use cyclosporine, in other words, somebody with a little bit of renal dysfunction who has got persistent afferent blood flow on the basis of prostaglandin.

Now, this is a nonsteroidal issue and not necessarily a cyclosporine issue, but the same kinds of physiology is going on here.

DR. WHELTON: But you are correct, that individual aged in the 30s, and perhaps 190 pounds with a serum creatinine of 1.7, that is renal impairment. That is not in the normal range, and I think by definition, by what we are driving

towards, one would not suggest such treatment for such an individual.

DR. JOHNSON: Are you saying you can essentially ignore the renal loss that is reflected by going from two-thirds to one-third the normal GFR, because I think that is what Dave is nervous about.

DR. WHELTON: What I am saying that it is a phenomenon of the aging process in somebody who is --

DR. JOHNSON: Leaving that aside, if you just take a normal individual, what you are going to say is that you calculate the creatinine clearance, and if it is greater than one-third of the normal range, then, you can give cyclosporine, correct?

DR. WHELTON: No, I didn't say that.

DR. JOHNSON: I think some people were interpreting you as having said that. That is what I was trying to clarify.

DR. WHELTON: I see. Well, one would really need a nomogram or the Cockcroft Gault type calculation, which will give the typical upper and lower ranges for GFR, glomerular filtration rate.

DR. CHAMBERS: So, how much loss would be allowed? What I have been hearing is that the committee is comfortable with the normal range, and that may be adapted by patients as long as it is within their normal, and there

is no tolerance above normal, because it has not been studied.

DR. PETRI: Correct, and this is taking into account the issues about the RA patient who has had muscle wasting, and the RA patient is elderly.

DR. CHAMBERS: There may be some corrections necessarily to figure out what the normal is for that individual, but we still want normal.

DR. WHELTON: And that is really what we are driving at. If one were to biopsy in somebody in the 80-year age range, they will have changes on biopsy, but that has to be accepted as part of the aging process.

DR. PETRI: Let's move on to the second part of the labeling. I don't think it is emphasized here under rheumatoid arthritis, which is the issue of how hypertension is to be managed. Some of the issues about hypertension follow on the next page under "Precautions."

Starting again on page 2-13, where we were looking at autoimmune diseases/rheumatoid arthritis, moving on to page 2-14 under "Precautions," there is a long section on hypertension, but that is actually sort of divorced from this section on rheumatoid arthritis. I actually would feel more comfortable if there was a section on hypertension and its management specifically under the RA part of the label,

and I would like to open that for discussion.

Dr. Chambers, you are frowning. What is your question?

DR. CHAMBERS: I am just asking people to remember this label, this is an additional indication it is getting added. I mean are we talking about writing, that there is not going to be one label, it is going to be three different labels, one for each of the additional indications that we have? In some aspects, it will be the same as the transplant sections. We usually try and only separate those when the population speaks that it should be separated.

DR. PETRI: Dr. Simon?

DR. SIMON: I would actually argue that given the risk/benefit ratios that we have alluded to already, that in the circumstances of transplantation, it is a very different issue about what the tolerance lines would be regarding both kidney function and hypertension as to attain or sustaining a transplant versus this circumstance. That is the way I would argue it.

So, under those circumstances, I would like it to be addressed differently even though you really are just extending the indication, but under these circumstances it is a very different patient population, and I would agree with Dr. Petri that -- in fact, I would go so far as to suggest that since hypertension has something to do with

kidney function, I would like to see that closer together, because I don't actually know how to separate the concepts from each other, and I think that they are interrelated, and I would like to see them very closely opposed to each other.

DR. CHAMBERS: I am not speaking that we have to do it one way or the other. I am asking the question, though, which way do we think --

DR. SIMON: That is what my answer would be to that.

DR. PETRI: I think the issue is that the nephrologists or transplant surgeon know how to do this? They have been doing it a long time. Rheumatologists don't know as much about it. I think we should be as specific as possible about the problems they are going to run into. For example, the interactions with different antihypertensives, I think should be highlighted in the section on rheumatoid arthritis, otherwise, I am afraid it is going to be missed.

Let me ask for the committee's opinion on that. Felix.

DR. FERNANDEZ-MADRID: I think in the section on hypertension, specific blood pressure levels should be mentioned to indicate that levels of 140/90 should be treated.

DR. PETRI: Dr. Luthra.

DR. LUTHRA: I was just going to comment that I think we should really have this as a separate section, and not

mix it with the transplant data because it is not just the nephrologist and rheumatologist, the patients are going to read it, and you are going to have all kinds of questions raised. A lot of these decisions have to be made judgmentally. With methotrexate, we get all kinds of questions regarding malignancy use and RA use. It's the same situation here, and I think a separate section on RA is important.

DR. PETRI: Other comments about hypertension? There is agreement that 140/90 should be specifically listed as the level at which to treat.

DR. SIMON: Could I ask a question?

DR. PETRI: Dr. Simon.

DR. SIMON: Are you suggesting, Felix, that you would do two things - one is that anybody who has a blood pressure at baseline of 140/90 and above could or could not be treated, number one, and if they were treated, you would immediately treat their blood pressure changes along concomitantly with the use of the Neoral, and that if they developed hypertension during the therapeutic intervention, you would then also treat, and that cutoff point would be 140/90?

DR. FERNANDEZ-MADRID: That is my intention.

DR. PETRI: Other comments about the hypertension

section of the label? Dr. Whelton.

DR. WHELTON: Yes, I would like to make the comment that the figure of 140/90, although a very reasonable and appropriate figure based on the general body of data available is simply a rule of thumb for an adult in general.

Since later on we are going to be dealing with the pediatric issue, again, there is this age correlation with changes in blood pressure, and we also have to be mindful that virtually all of the studies done prospectively in the world that have actually demonstrated an important benefit in morbidity and mortality have been with diastolic pressures of 95 or greater. So, we may want to make a cautionary note to just say as recommended by the Fifth Report of the Joint Commission on detection and management of hypertension da-da-da-da.

DR. PETRI: Dr. Abramson had a comment.

DR. ABRAMSON: I just have two questions about the drug interactions that are listed here on line 323, just in terms of the clarity of the language. It says, "Interference with cyclosporine metabolism by calcium channel antagonists may require dosage adjustment."

I assume that means that you will have increased cyclosporine levels, but I think it is not clear necessarily in reading that what you should be thinking about.

DR. PETRI: I would agree. Any comments like some of these drugs, it would be so much easier for the rheumatologist reading this to list them. Other comments about that wording? Dr. Pucino.

DR. PUCINO: In terms of the hypertension, just to mention the percentage of patients, it would be nice for the prescriber to know the percentage of patients who have persistent hypertension even after stopping treatment, such as 25 percent staying above 160/95.

DR. PETRI: So you would like an elaboration of what the risks were in the clinical trials done to date.

DR. PUCINO: Right, this being a persistent complication.

DR. PETRI: Let me ask Dr. Chambers and Dr. Johnson. Is that possible in labeling to give more exact information about the clinical trial results?

DR. CHAMBERS: It is certainly possible. You start getting into the balance, and we will be relooking at the label after we have the comments about what is readable and what now becomes a textbook for which people are not going to read, and generally try to make it sufficiently succinct, so that it still is readable.

DR. PETRI: I think our general consensus is that what is now listed under rheumatoid arthritis is probably too

succinct, and there is going to be a happy medium.

DR. CHAMBERS: Agreed, and that is why we will ask for the comments, and we will go back and rework this at that particular time, but I also ask that people recognize that there is a balance, and you can get too much.

DR. PETRI: Dr. Simon.

DR. SIMON: But even with that balance, with the idea that you don't have a total reversibility here of hypertension, that there is intrinsically in that message damage that has taken place, that has caused a permanent situation where 25 percent or whatever the data demonstrates have persisted in hypertension even when the drug is away is very different than the implication that one gets that when one is on a drug, and they become hypertensive, that perhaps, although it is never stated, that when you stop the drug, the hypertension may go away is the concern that I have by not stating the obvious, that if, in fact, there is 25 percent of the patients that had irreversible changes leading to sustained hypertension, that may even preclude people from using the drug before they even start. So that is why I think it is so important to include that information.

DR. CHAMBERS: I am not saying we would not include it. It would be included in either the adverse reaction section

as reversible hypertension and/or in a precaution section, not necessarily in the clinical trial section.

DR. SIMON: I understand.

DR. PETRI: Yes, Dr. Abramson.

DR. ABRAMSON: I am sorry. There is one other question. I don't think we have heard about the use of ACE inhibitors with cyclosporine and its effects on potassium, and whether that should be addressed in the hypertension section.

DR. PETRI: Dr. Torley.

DR. TORLEY: We actually only had one patient in whom ACE inhibitor was the treatment that was used. I would like to defer to my transplant colleagues who have a lot more experience with ACE inhibitors and the control of cyclosporine hypertension.

DR. CURTIS: ACE inhibitors have been used extensively in the transplant experience also. There is a slight tendency, not clinically significant, for them to decrease GFR slightly.

Long term, while the calcium channel blockers seem to make more obvious sense, and that they vasodilate at the same area where cyclosporine vasoconstricts, the long-term clinical trials have shown equal efficacy in terms of blood pressure reduction with ACE inhibitors and calcium channel

blockers.

DR. ABRAMSON: No adverse effects on potassium?

DR. CURTIS: There is additive, but not enough that many people get into trouble with hyperkalemia. It adds to the difficulty with potassium secretion, however.

DR. PETRI: Dr. Simon.

DR. SIMON: Maybe I am overstating the obvious. That population isn't given nonsteroidal anti-inflammatory drugs as regularly as our population is.

DR. CURTIS: That is correct.

DR. SIMON: The combination may actually be not.

DR. CURTIS: They are given nonsteroidals on occasions, but not like your population. They do run into, however, other drugs on occasion.

DR. SIMON: I do understand that, not to suggest that these are healthy people necessarily, but the issue of ACE inhibitors along with nonsteroidals in particular is one of some concern to us, as well.

DR. APPEL: When we switched to cyclosporine years ago, people were going home on Kexlate and other things to lower their potassium, but it brings up an issue that is probably going to be more important in the future with the A2 receptor antagonists coming out.

Losartan is already available and I know there is work

on erbosartan, eposartan, and valsartan now, so given this, we are going to have as many sartans as prils, and there will be many A2 receptor antagonists, and supposedly from the controlled trials, there is less hyperkalemia with the sartans, so leaving an open range for practicing rheumatologists to use these would be good, I think.

DR. CURTIS: The other -- and this is speculation also -- the other reason why ACE inhibitors are used is there is some speculation they might mitigate the nephrotoxicity also in terms of mechanistic causes. That is not proven. They are also used quite a bit in transplant for what is called posttransplant erythrocytosis, a problem you don't deal with.

DR. LOVELL: As I am sitting here listening, I mean what the label says is treat with antihypertensives, period. Now, we all have the luxury of having transplantation specialists, nephrologists, rheumatologists with extensive background.

Is it really wide open other than the calcium channel blockers being shown to change cyclosporine metabolism, is it wide open, is a beta blocker just as good as calcium channel blocker, or should there be some indications, as Michelle has suggested, to the run-of-the-mill rheumatologist or, God forbid, a pediatric rheumatologist

who has never done a transplant, as to which antihypertensives should be used?

DR. CURTIS: The logic would dictate the so-called renal sparing or those antihypertensive medications that result in renal vasodilatation and increased renal blood flow. That would fit nicely with it, and I was glad to hear people suggesting that the kidney and hypertension are tightly linked together. There are some groups who might not say the link is quite so tight, and as Dr. Torley pointed out, there is a role of the sympathetic nervous system.

So other types of antihypertensive medications have also proven effective, but in the transplant community, at any rate, there has been a concentration on renal vasodilators including calcium channel blockers and ACE inhibitors and losartan.

DR. PETRI: Dr. Whelton.

DR. WHELTON: I just have to add in a cautionary note about the ACE inhibitors, that in general, for example, a big group where they are indicated for glomerular protection in diabetes, a serum creatinine of 2.5 is an absolute recommendation not to use them because we will see drug-disease interaction.

Now, if we are recommending that the drug pertinent to

rheumatoid arthritis only be used in those with normal renal function, I wouldn't have genuine concern. If there is an extension to say, if we make some commentary about ACE inhibitors and that they are going to be a safe and logical selection, I think there would have to be an additional disclaimer to say that in the setting of renal impairment, there may be drug-disease interaction.

DR. PETRI: Dr. Simon.

DR. SIMON: In fact, maybe we should go so far as to say since we have seen data on beta blockers and calcium channel blockers, and if we use the same thematics we have done before, we don't have data about anything else, we should just specifically say that, that antihypertensive therapy with beta blockers and calcium channel blockers works and should be pursued, as to whether or not you can use ACE inhibitors and yada, yada, we don't know, and maybe perhaps the registry would address that.

DR. PETRI: Again, as long as there is that caveat of those calcium channel blockers that are going to affect the drug level. I think we have reached a consensus about our recommendations about hypertension.

Yes, Dr. Liang? I think we had several concerns that 140/90 should be the blood pressure at which treatment was instituted, that hypertension drugs would be specified in

greater detail than they are in the current label. I realize that some of this information is under Precautions, but we wanted it moved up under Rheumatoid Arthritis.

DR. LIANG: What I am hearing is a lot of anecdotes. I don't hear data about things other than calcium channel blockers.

DR. SIMON: And beta blockers.

DR. LIANG: That is also an anecdote, isn't it?

DR. PETRI: No, the beta blockers come from the clinical trials.

DR. LIANG: I don't think we should dignify the anecdotes by writing it.

DR. PETRI: I agree.

DR. LIANG: The other thing is I am sort of uncomfortable about this whole, you know, paint-by-numbers kind of approach that we are doing here. I would just as soon have it, you know, this is a hot drug, don't let the gorilla out of the cage unless you know what to do, send them to a nephrologist who has more experience than any rheumatologist using cyclosporine rather than trying to give all these little caveats that almost gives you the mood that we have this thing under control.

DR. APPEL: This is going to be an unusual comment, but here is the rheumatologist saying to send them to a

nephrologist, and I am a nephrologist saying keep them. In this day and age, that is unusual, but the answer would be is that maybe if you are uncomfortable in terms of dealing with renal function hypertension, but after a short while, like the nephrology community, you will become very comfortable in terms of treating the hypertension, and once the person is comfortable with it, I see, you know, maybe as long as they are dealt with, with somebody who has experience with the drug, and I would assume most rheumatologists would gain experience.

DR. LIANG: At some cost.

DR. APPEL: Well, it is better a rheumatologist at some cost than general internists and family practitioners at a much greater cost with much less experience.

DR. PETRI: I think that was one of Dr. Simon's comment, that we want to be very specific who is going to have enough expertise to be able to manage these patients, but I think for the most part, rheumatologists have to get to know this drug.

DR. LIANG: I don't think we have to be sectarian about this. I mean there are a lot of people who use cyclosporine probably that aren't rheumatologists, but I think the key is just expertise and comfort and also availability of consultation if they feel uncomfortable with it. But I

don't think we can make this thing so prescriptive that we are going to keep people out of jail or patients out of trouble. I mean I think putting numbers down just gives an illusion of specificity that doesn't exist.

DR. PETRI: I think if we can give some guidance, some guidance is better than none.

DR. LIANG: You guys will have to deal with the texture of it, but I think that sometimes when you put down numbers --

DR. PETRI: Dr. Abramson had a comment.

DR. ABRAMSON: Just along those lines, the warning that now exists in the package insert does say that the drug should be used by physicians experienced in immunosuppressive therapy. Is that warning going to stay and be applicable to the rheumatoid arthritis patient? I suggest it might be a good idea.

DR. CHAMBERS: This is the starting label we are starting with. We will take comments that we hear today, we have internal comments that we will also go through, and we will discuss things with the company, but we are interested in any comments you have in any sections.

DR. PETRI: If I have sufficiently stated the consensus on hypertension, I had some comments this morning under malignancy that I thought the basal cell carcinoma and

cervical carcinoma data should be highlighted since they are numerically more frequent than the lymphoma data.

Dr. Torley, this morning you agreed with that. Did you have any comments this afternoon?

DR. TORLEY: I think in terms of basal cell carcinoma, it certainly was the most frequent malignancy we have seen. The comment Dr. Curtis had made about transplantation, about cervical cancer, did relate to the transplant population.

We haven't actually seen more than I think a maximum of two cases in the RA population, but I certainly think there does appear to be an increased risk at least of basal cell carcinoma at this point, so I don't think a caution in the label would be inappropriate.

DR. LIANG: I just wanted to have reassurance that you looked at the other malignancies with respect to their expected rates. I mean I didn't hear a specific answer to that question.

DR. TORLEY: Actually, perhaps I can ask Dr. Strom to comment. One of the difficulties we have is understanding what the expected incidence rate for these other malignancies would be, and that is very difficult to comment upon.

DR. LIANG: That data is available. I just want to know if you did the computations and looked at them.

DR. TORLEY: We looked at it in 1992. At that time, basal cell carcinoma was the one. That analysis hasn't been updated any more recently than that.

DR. LIANG: But you looked at the other malignancies?

DR. TORLEY: At that time, they looked at all malignancies, but we haven't look at it based on the data I showed you today.

DR. PETRI: Are there any other additional comments or questions of the committee about risk/benefit, safety issues before we move on? Dr. Chambers.

DR. CHAMBERS: Before we leave that, is there a reason to believe that cervical cancer would be different in the transplant population than the RA population as far as cyclosporine is concerned? I mean is there is an increased rate in the transplant population?

DR. CURTIS: The transplant population, again, they are exposed to many more immunosuppressive drugs. There are a lot of studies about HPV virus in transplant population. I don't know that that has been studied in the rheumatoid arthritis population.

DR. CHAMBERS: So, you are suggesting the cervical is not due to cyclosporine, it is due to something else?

DR. CURTIS: Well, total immunosuppression and viral infections that are common in this end stage renal disease

population.

DR. JOHNSON: I think you can go even further, too, if you subdivide transplant into renal versus everything else, the rates are higher in the non-renals, because you are trying to save the patient rather than just losing the kidney.

I thought historically, the best myeloproliferative data is the old Imuran studies. There is about six or eight of those, and with various degrees of confidence in your denominators and enumerators, but when you lump them all together, you know, you get this impression that the incidence of non-Hodgkin's is up slightly in rheumatoids, and, of course, it goes up a little higher with Imuran.

The odds are something like that is going on here, too, but the registry you guys have has a lot of instability in both your enumerator and denominator, so I think we have to weigh with a grain of salt any conclusions that we draw from those numbers.

DR. PETRI: Dr. Felson.

DR. FELSON: I don't know if this is the appropriate time to raise other concerns about the label, but it would be nice -- going back to your earlier concern, Michelle -- that some note of cholesterol elevation on this drug be placed in this package insert, so people who have baseline

high cholesterols are on treatment for it. You know, at least the doctor who is putting them on it knows that this is something they need to consider in using the drug and maybe following closely.

DR. PETRI: Thank you.

Let's move on to Question 2, which is the indication section. The first question is in which set of rheumatoid patients. Obviously, this is getting at the issue of monotherapy, does someone need to fail first another drug, and if so, which drugs.

I think this is an important enough section that we may actually go around the panel.

DR. LOVELL: Have we, as a committee, satisfied ourselves that we have addressed the long-term renal issue? Are we going to come back to that?

DR. PETRI: If you would like to bring it up now, I think we do have a general wish to have post-market surveillance. This might be a good time just to address what things we think are essential as part of that. Do you want to start?

DR. LOVELL: I think I just wanted to raise the question. We have spent a lot of time kind of addressing short-term issues in terms of creatinine clearance, and that sort of thing, but I still think we ought to at least make

our wishes known about long-term toxicity, and I don't think I am the best person to talk about that, but I think it is an unanswered question that isn't addressed very thoroughly by the existing database.

DR. PETRI: Additional wishes that should be part of that post-market surveillance? Dr. Simon.

DR. SIMON: Given the fact that there is this tendency to think that we know a lot about this because it has been out there for so long, particularly in the transplant population, my concern is that this is really a different patient population, so I would like to start a little bit from scratch and ask what are the things that we know about the drug and as it relates to over time, why would we care about it.

One is kidney function, one is blood pressure, and the issues by regression analysis, how blood pressure plays a role with kidney function issues. I would like to know really about all the things that happen to these people over time and as particularly relates to malignancies, as well, be it basal cell carcinoma, the incidence of cervical carcinoma, or other kinds of malignancies that can only be gotten under these kinds of very careful collection databases.

Now, I don't know if it requires biopsy data in a

prospective manner as opposed to just collecting it as it goes along and have stringent requirements to ensure that the data is collected well and is useful, so that at the end of five years we can look back and actually think about what it might mean, but I do think it is the big issues of blood pressure, kidney function, and malignancy that we are interested in, as well as all the other potential toxicities that might be unique in this patient population, and it may not be correlatable to transplant patients.

DR. LOVELL: I have a question for Kent. Would it be sufficient from your perspective if the committee were just to voice a concern about the need to get long-term renal toxicity data in this patient population and leave it up to you and the sponsor to kind of figure out the details of a post-marketing surveillance study? Would that fulfill the need for you and be more productive in the long run?

DR. JOHNSON: I think the more feedback, the better. It is tricky, you know, when you really start getting down to details what hypotheses you want to address, to what degree, to what competence do you want in the conclusion, and blah-blah-blah, and you can rapidly get into something that is infeasible.

We could always say, well, how does this compare historically to prior approved DMARDs and so on. We didn't

have the hepatotoxicity thing worked out with methotrexate, but the ACR actually helped in that regard, you know, over time, with some instability in their numbers, too, I suppose, but I mean there were major problems with proposals to study anything systematic, let alone with a control. I assume everyone is talking about open observational studies here with prn biopsies if you are in trouble I suppose

I have thought about this, but we want feedback from the rheumatologists who have to look at patients over five, 10, 20 years.

DR. PETRI: Dr. Whelton.

DR. WHELTON: I would be very doubtful that any human investigation committee would sanction doing routine follow-up biopsies, renal biopsies in such individuals. That then would say one would have to continue these studies under the aegis of an IRB, and I think we certainly would want to get away from that.

I mean there is no doubt it would be incredibly desirable to know how many had a change in renal function, how many developed hypertension, what was the change in their urinalysis, did it get better when the drug was stopped, all the things that any one of us could think about, but mechanistically, can you do it.

DR. JOHNSON: I am sure you are right. Just take a

simple proposal. Take a proposal that you are going to serially enlist -- and I think it would probably have to be serially enlisted to avoid cherry-picking at the front -- you know, 300 patients and follow them for five years.

I mean the mechanics of that are tricky, you know, and the dropouts can destroy any conclusion even after a year's time, let alone after five years' time.

DR. TILLEY: For cancer, if you have got enough basic information, you could at least follow people who live in areas where there are cancer registries, so because 300 people for cancer would be hopeless.

DR. JOHNSON: Cancer, I think we should deal with separately. If you really want to get a handle on what goes on with a creatinine of 2.0, and you start them on cyclosporine, or if you start them on 1.5 and it goes up to 2.0, and you don't want to stop it, what goes on with those patients, I mean I think those are important questions, and I would be interested in whether you think there are ways to get answers feasibly.

DR. LOVELL: Well, we don't have any data as to what happens if you start it with a creatinine of 1.2 and wait five years, correct?

DR. PETRI: We have two years.

DR. LOVELL: Right, so you don't have to extrapolate it

to the extremes of creatinine. I mean you could put it right in the middle of normal creatinine. We are really in the dark as to what happens with this drug and the kidney after more than two years.

DR. PETRI: Felix.

DR. FERNANDEZ-MADRID: I wonder if there is a cautionary note on the use of nonsteroidals that may increase the renal toxicity of cyclosporine, and the possible impact of this on diminishing the clearance of methotrexate. Is there such a cautionary note?

DR. TORLEY: Yes, there is. As I stated this morning, we do comment on if you change the dose on nonsteroidals or change a nonsteroidal, you should increase the frequency of the monitoring.

We also caution specifically about the concomitant use of diclofenac with cyclosporine because of the theoretical risk because cyclosporine increases the area under the curve for diclofenac by 100 percent, there might be a theoretical risk, and we do advise that the lowest dose of diclofenac is the dose that is used.

DR. FERNANDEZ-MADRID: However, analysis for each of the nonsteroidals has not been done.

DR. TORLEY: No. The only analysis we have compares diclofenac versus all other nonsteroidals versus no

nonsteroidals, and we saw no significant differences between the degree of increase in creatinine SGOT or SGPT, between those three groups, but we haven't analyzed by any further nonsteroidal subgroups.

DR. LOVELL: I couldn't find in the label anywhere mention of the effect of cyclosporine on methotrexate. Perhaps I missed it, but I couldn't find it, and I think in the setting that a lot of these patients are going to be on more than 15 mg/week, that we probably ought to put that in somewhere.

DR. PETRI: Okay. Let's move on to Question 2, so we don't shortchange that. The major focus of Question 2 is which set of patients are going to be appropriate. I would like us to very specifically address the issue of can this be initial monotherapy.

Dr. Felson.

DR. FELSON: Actually, I was going to offer to start to address that question because it seems like we need to move on. I actually think the package insert is fine, and I wanted to suggest that with respect to what subsets of patients ought to be treated, the package insert says that it is indicated for treatment of patients with severe active RA in whom at least one slow-acting second line drug is ineffective or nontolerated.

Then, it says can be used in combination with methotrexate who do not adequately respond to methotrexate alone. I think after or at some other place, I would put something like -- and this addresses part of Question 2 -- an interaction with methotrexate is possible, and it's, you know, something to the wording of an understanding of this interaction is currently unknown, but there would be concern about using these two in combination for fear of an interaction.

DR. LOVELL: But at least you ought to put in that wording which way the interaction goes.

DR. FELSON: Yes, fine, that the combination may be, in part, effective because of an increase of methotrexate levels or something like that.

DR. LOVELL: I wouldn't get at the effectiveness business because we don't know that, but I would at least reflect the fact that existent data has indicated that cyclosporine increases the methotrexate levels.

DR. PUCINO: I don't know if there is a way it can be specified. Again, I don't want to get too specific on this, but the fact that the information is only again up to 15 mg, and it is not uncommon that the dosing is going to be used above that, and to say that the long-term toxicity with doses greater than 15 mg is unknown. Once again, just to

inform who is using the drug.

DR. PETRI: Again, you have to be careful because the long-term toxicity is unknown, period, but there would be a special concern in patients who are taking greater than study doses of methotrexate.

DR. LIANG: I don't like the wording because at least in our center, we have a fairly high volume of practice, I don't think anyone is moving to it right after just one failure of a DMARD.

DR. PETRI: For example, David, do we really mean failing hydroxychloroquine?

DR. FELSON: Well, do you want to put failure of methotrexate, because that is really the standard of therapy now?

DR. LIANG: At least one slow-acting second line is -- you know, I haven't had a patient that I have followed that hasn't had one failure to slow acting. That is why I don't like the wording here. Is that what we mean?

DR. FELSON: Let's be specific. Do you want to make it two or three?

DR. LIANG: Well, I think that is for discussion, but I think the wording isn't good.

DR. FELSON: Personally, I wouldn't disagree with that. I think, you know, to think of somebody failing

hydroxychloroquine and then moving to this drug would be inappropriate, and I would certainly want to discourage that. You know, if a physician looked at this package insert and said, oh, yeah, they failed hydroxychloroquine, let's move to cyclosporine, that wouldn't be right.

DR. LOVELL: Well, the patients in the database that failed on average, what, three, a little over three other second-line agents, is that right, two or three, something like that?

DR. TUGWELL: On average, but there were quite a few people who had only failed one. I just wonder whether it might be possible to consider those who failed methotrexate, so we don't have the hydroxychloroquine issue.

DR. LIANG: I think in the real life practice, you could still move to something else. I mean this is an order of toxicity, you know, I think this should be one of the latter ones to try. I mean sulfasalazine, I think would be far safer and gold maybe. I think that is the way I sort of use it.

DR. PETRI: Dr. Hochberg?

DR. HOCHBERG: If I could, I would like to make a comment on the use of this in clinical practice. Some of us stage patients with rheumatoid arthritis the way oncologists stage patients with cancer, and the patient with moderate to

severe rheumatoid arthritis goes directly on methotrexate.

It has been suggested by a number of panel members if that person has an inadequate response to full-dose methotrexate, a number of us are now adding cyclosporine to that methotrexate background, so they haven't yet -- they have really failed one second-line agent, or if they are intolerant to methotrexate, but if that patient has severe disease, already has nodules, erosions, et cetera, a number of us aren't going to bother with hydroxychloroquine or sulfasalazine.

DR. LIANG: Well, I think this is like cooking. You know, this is not a democracy, but I don't think that that is probably the normative pattern in my area, let me put it that way, especially with the New England Journal article about triple therapy using noncyclosporine triple therapy.

DR. PETRI: Dr. Abramson.

DR. ABRAMSON: I share the concern that this drug should be used after hydroxychloroquine, but I think my instinct is that if we write this package insert right, and we show the pitfalls of the potential toxicity of this drug, and we leave it to the ACR and the organization to give us practice guidelines, I don't think that this organization should get into putting hierarchies that are very specific to what order we use these drugs, because that is subject to

change. I think this will be a rather sobering kind of package insert that I think that the good physician will follow if we use the drug not right after hydroxychloroquine.

DR. PETRI: Are we back to the consensus that we are happy with the indications for use as currently written? I have at least one dissension from Dr. Liang. Are there others who wish to dissent and state their reasons? Felix first.

DR. FERNANDEZ-MADRID: Well, I think I share these concerns. I think what we have heard, it is what many rheumatologists do. Some of us do this, others don't do this. There is a lot of anecdote in this.

I think I have a lot of problem with a methotrexate-stuck patient. I think if this study had been done 10, 15 years ago, we would not be discussing the introduction of this drug very early in the treatment of rheumatoid arthritis.

We would be discussing this as an add-on after other safer DMARDs have been used, but since methotrexate has taken over the field and has proven that it is a safe and effective drug, but some patients do fail to methotrexate treatment.

We call them partial failure and sometimes it is our

wishful thinking that methotrexate is still doing something, we add something to this, and this is the rationale to use this drug on top of methotrexate on this methotrexate-stuck patients.

I have no problems with the efficacy and safety profile of this drug as a monotherapy, but I have a lot of problems with the concomitant use of these drugs together with methotrexate in these patients, and I feel that it is rather paradoxical that it is, at least the label says, to treat severe active rheumatoid arthritis.

I think this implies a silver bullet, but we have learned that it is not a silver bullet, and I would eliminate the severe from the label because its action is a moderate action. It sounds like a very useful drug, but its action is moderate.

DR. PETRI: Dr. Simon.

DR. SIMON: Well, I would actually argue that your argument would have led me to underline the severe rather than take it out, and that is not based on its efficacy, that is based on this risk/benefit ratio more than anything else.

What I am going to say is not to suggest that I don't think this drug works. I think that this is a very important new addition to our armamentarium, but I am

distinctly unimpressed that we are dealing with a drug that will actually cure anybody and has significant risk factors.

So, I would agree with Matt that the way that it is presently written we are leading us down a path which will give this drug earlier to people that might not benefit from potentially safer drugs because they won't get a chance to be exposed to them, and if this drug had any evidence that it altered erosive disease with the biologic nature of this disease, I would feel very differently about where it should be positioned, but since we have seen no data about that and no evidence about that, and there are no claims being made about that, I would argue that this drug is on the scale of toxicity potentially very toxic, and under those circumstances, would like to see it after other drugs have already been failed.

I think that David's last comment that suggested perhaps in relationship to Matt's comment that it would be usable after someone has failed hydroxychloroquine da-da-da, methotrexate, and perhaps in combination with methotrexate, I would be very comfortable with that kind of statement.

DR. PETRI: Dr. Hochberg.

DR. HOCHBERG: Dr. Petri, might I show the indication for azathioprine?

DR. PETRI: Yes.

[Slide.]

DR. HOCHBERG: Adult patients with classic or definite rheumatoid arthritis restricted to "those with severe active and erosive disease not responsive to conventional management... or to agents in the class of which gold is an example."

A number of us would be concerned about the toxicity of azathioprine with regard to immunosuppression, infection, neoplasia, et cetera, hepatotoxicity, pancreatitis, and a number of others, so I just show that as an example.

DR. LIANG: That is very nice but there is an "s" on agents.

DR. PETRI: Are there additional comments from the committee? So, Drs. Chambers and Johnson, I think were telling that we don't have full consensus of the committee on this issue.

DR. LOVELL: Well, let's work with it a little bit more because I don't think we have reached a stalemate. I mean obviously, people aren't comfortable with it being given right after plaquenil, and I think Dr. Hochberg's comments were quite appropriate, that if methotrexate is the first one out of the block, that it would be reasonable to add cyclosporine in severe patients.

The patients who don't have very severe disease, could

we say that they have failed at least two other second-line agents other than methotrexate before they get put on cyclosporine?

DR. SIMON: As long as one of them is methotrexate?

DR. LOVELL: No, they don't have to fail methotrexate. They could fail hydroxychloroquine and D-pen and then be eligible for cyclosporine. I am just asking the question. I mean methotrexate, I think for most people is the first one out of the block, but not necessarily so, but we don't want to necessarily say cyclosporine will be right in around after plaquenil, but I am not sure that we should have to require a patient to fail methotrexate before they get put on this medication, so you could give kind of two avenues. One is methotrexate failures or patients who have failed two second-line agents other than methotrexate.

DR. PETRI: Dr. Felson.

DR. FELSON: I am sort of trying to move to figure out how we could arrive at a reasonable consensus here, and it strikes me that the azathioprine example was nice, and that it reminded me that the standard of care at the time when azathioprine was released was gold, and the standard of care in rheumatoid arthritis now -- and I think all of us in the room who practice adult rheumatology would probably say the patient needs to be tried on methotrexate for a while before

you would ever consider using cyclosporine.

I think based on prevalence of use and based on good data, the standard of care in rheumatoid arthritis for second-line drug treatment is methotrexate, and I think what we should include here is a statement that perhaps use of methotrexate is one of the things that they need to fail or not do well on, maybe even another, you know, say, look, patients have got to have failed methotrexate and perhaps one other second-line drug before you use this drug, because you could say, Dan, well, give them hydroxychloroquine and D-pen, and I don't think, honestly, that is not a reasonable trial of second-line drugs before getting to cyclosporine. Methotrexate has got to be in that mix somewhere.

I think that is something almost everyone would agree on at this point. I think that consensus is valuable. Matt doesn't agree with that consensus.

DR. LIANG: I have worked long enough I guess to tell you that I have had patients who have done all the usual suspects and respond to hydroxychloroquine or sulfasalazine, so I don't think it's right for us to dictate the order of trying these agents, especially since there is no demonstration on structural damage here.

I like the wording that says you have tried other things and gave it a hard run, but I don't think we can be

so prescriptive about when and which drug we are going to follow with this agent.

It is very new in the experience. We have 2,000 patients that we know something about and 20,000 patients that are sort of out there doing something, but this is a very costly drug, and it is really hot, and it is tough to monitor. So, I think we should let that judgment fall onto the patients and physicians who want to make the decision, but we shouldn't shackle them to some rigid sequence.

DR. SIMON: But it would be after -- but you are arguing that it would be after some set of other drugs that would be tried first.

DR. PETRI: Drugs with an "s" because that is where we ran into the hydroxychloroquine problem.

DR. SIMON: Drugs with an "s" beforehand.

DR. PETRI: So this is our best attempt at a consensus, that the patient should have failed several drugs with an "s" or failed methotrexate.

DR. FELSON: And at least one other, something like that.

DR. PETRI: I am willing to say or failed methotrexate, period.

DR. CHAMBERS: Is it just methotrexate or --

DR. PETRI: No. We reached a consensus only on the

first clause, which has failed several drugs with an "s."
Is the feeling that it has to be methotrexate and another
drug as well? Comments from the committee.

DR. ABRAMSON: I don't think so. I personally think
that may be too restrictive. Marc Hochberg's approach to a
patient would not then be allowed under that kind of
scenario. So, I favor drugs or methotrexate, but
methotrexate perhaps could be the single agent that is in
the original package insert, to stand alone as a failed
drug. Otherwise, I think we are overlegislating what
physicians can do.

DR. CHAMBERS: We can leave it as a disagreement, that
is fine.

DR. PETRI: I think we are very close there. Is there
actually strong dissent to failed methotrexate as the second
clause? I think we are very close to consensus on that.

DR. LOVELL: Let's vote on maybe failed two other
second-line drugs or methotrexate.

DR. PETRI: If you agree with that statement, would you
please raise your hand.

[Show of hands.]

DR. PETRI: Dissenters, please raise their hand.

[Show of hands.]

DR. PETRI: Well, it passed, but I would say there was

not unanimity.

We are asked several very specific questions here. The first one, Part (a), is should separate recommendations be recommended in the presence of background methotrexate.

Is there discussion?

DR. SIMON: I am not sure I understand that as it relates to this previous discussion.

DR. PETRI: It may not follow right after our previous discussion, but we are talking about that increase under the curve.

DR. SIMON: So we are talking about toxicity.

DR. PETRI: There is a 30 percent increase in methotrexate when it is given in combination with cyclosporine, should that change the package insert.

Dr. McGuire.

DR. MCGUIRE: The implication is concurrent methotrexate or preceding treatment with methotrexate?

DR. PETRI: Concurrent.

DR. MCGUIRE: Then, I would change the language.

DR. PETRI: I don't think we actually saw any data that there was any increase in adverse events, so there was no clinical implication to concurrent use. Please, someone correct me if I am incorrect.

DR. WHITE: There has to be a dosage restriction, I

think. The same issue of they have only looked at it up to, I think, 15 in clinical experience, maybe 20 mg. The issue is you perhaps ought to put a cap on it.

DR. PETRI: Dr. Simon.

DR. SIMON: In addition to that, Patience, I think that we are naive to believe that some of these side effects that we might see in combination therapy, such as this, could be seen within a year of therapy, that we need to recognize that the longer term outcomes in this particular chemotherapy combination needs to take into consideration years, and that is why the registry becomes so important, so identifying that we don't know is a reasonable thing to say at this juncture.

DR. PETRI: Additional comments? I believe our consensus there is that there needs to be a clear cautionary note that there is no data on the use of more than 15 mg of methotrexate weekly.

DR. SIMON: Or whatever time period.

DR. PUCINO: A comment.

DR. PETRI: Yes, Dr. Pucino.

DR. PUCINO: In terms of the methotrexate, the increase in the area under the curve, do we know an age difference in terms of cohorts, young versus old cohort with the difference?

DR. CHOC: Well, we have not done a formal analysis breaking down by age, but these were rheumatoid arthritis patients, I think the average age again was over 50.

DR. PETRI: We have sort of moved into the next question, Part (b), which is, is there a significant PK interaction with Neoral and methotrexate.

I thought it was pretty obvious that there was a 30 percent increase under the curve. I may be missing the point of that question.

DR. JOHNSON: There was an increase in the drug and a decrease in the 7-hydroxy form of it, neither of which we know the relevance of.

DR. SIMON: We don't have a clue whether there is or isn't.

DR. JOHNSON: That is why we are asking. Steve, your group has published on methotrexate mechanisms of action. Do you want to make a comment on this?

DR. ABRAMSON: I don't know what the 7-hydroxy form does, what its biologic activity is, so I can't really add anything to the discussion.

DR. PETRI: I think Felix had a comment.

DR. FERNANDEZ-MADRID: I don't have anything. I have a question. These PK studies on interaction of Neoral and methotrexate, have they been done also in the presence of

nonsteroidals?

DR. JOHNSON: Does one of the PK people want to address that?

DR. CHOC: I don't remember the exact incidence of nonsteroidals, but nonsteroidals were not prohibited in the study.

DR. PETRI: So there is a general concern that we probably need more data.

DR. LOVELL: But I am not sure it comes from them. We need to know better now methotrexate works, right? I mean it is not fair to put that on the back of this company. I mean we are ignorant about methotrexate in the presence or absence of cyclosporine of what these things mean.

DR. SIMON: But they have asked for an indication in combination usage, and so, therefore, it is still incumbent upon the sponsor to demonstrate that combination usage would be safe and doable and that there aren't unknown things happening because of that circumstance.

DR. PETRI: Dr. Pucino.

DR. PUCINO: One more question in terms of the kinetics. The drug is over 90 percent protein bound. Do we know anything about free drug kinetics both alone or in combination therapy?

DR. CHOC: No, we don't know. We did not measure free

drug in the study. We just measured total methotrexate and total 7-hydroxymethotrexate in plasma.

DR. SIMON: So now you can appreciate nonsteroidals. We know a lot about them.

DR. PETRI: The second part under (b) was is it clinically significant, and I believe the sponsor addressed that, that they cannot find at this point a clinical significance attributable to this.

Let me ask the committee if there were specific questions about that.

DR. LIANG: Short term/long term.

DR. PETRI: The only way we can address that final comment, if so, what are its implications regarding labeling. Right now there are no implications because there are very few data.

DR. JOHNSON: I guess the concern is what weight of evidence do you put on 70-odd patients, on co-administration drug versus methotrexate alone, because that is the only trial data we have.

DR. PETRI: Kent, I think the committee has clearly stated the need for post-marketing surveillance, and I think the special subgroup of that post-marketing surveillance has to be the patients who are on both methotrexate and cyclosporine.

DR. JOHNSON: Let me just put this slide up for a moment. It is going to be tricky if we relegate too much to post-marketing.

[Slide.]

Actually, I am just harping back to what we talked about a minute ago. If you look at just blood pressure and renal insufficiency as issues of concern, which I think they are, the near term use of the drug you can envision in four different fashions.

One is labeling the use with no problems or labeling the use with induced hypertension, labeling use with renal insufficiency, or off-label use where you put somebody with a creatinine of 2 on, and long term you have got various questions you might want to answer.

One is what happens vis-a-vis renal insufficiency and the sequelae of renal insufficiency, what is the outcome vis-a-vis blood pressure control and what are the sequelae, and the third issue is reversibility.

So, as you can see, you have already got about 12 possible questions there, I think, 4 times 3, but it is not to minimize the methotrexate issue. I think that co-administration with methotrexate is another problem that we have to talk about.

DR. PETRI: I think our concern is a 30 percent

increase in the area under the curve is going to translate 10 years from now in more hepatic fibrosis, more pulmonary problems, and I don't see any way that can be addressed without post-market surveillance.

DR. JOHNSON: Well, there is always a lot of unanswered questions, and I am not sure we can post-market survey for everything.

DR. PETRI: But I think a special use of this drug is going to be in combination with methotrexate. I think that is what Dr. Hochberg was bringing up. So, the post-marketing surveillance, I think has to capture that special use group who are going to be our sickest, most severe rheumatoids.

Dr. Simon.

DR. SIMON: We can't underline that more because, in fact, there is a specific identity of use in that regard. Part of the proposal here is to go along with the idea to use it in combination. It may well be a good thing to do, but we have no clue whether it is, in fact, safe. We have short-term data that tells us that.

If that is not the key issue or one of the key issues in some form of longitudinal follow-up, then, we are really not doing our job, and in fact, if this was an ideal world, you would have probably required to approval for that

particular use a three- to five-year study to look at that question, because that is, in fact, what you really want to know.

DR. PETRI: Aren't we dealing right now with just six-month follow-up on the combined methotrexate/cyclosporine?

DR. SIMON: Yes.

DR. JOHNSON: Six-month study period.

DR. LOVELL: Maybe we could play it this way. We have two indications here as we have kind of played around with our committee. One is the methotrexate combination indication, and the other one is kind of the alternative route, which is a couple of DMARDs.

It would seem to me, in terms of late toxicity, that methotrexate/cyclosporine would be the worst case scenario, so perhaps we could do a post-marketing surveillance study that would be limited to patients on combination therapy.

It would make it easier for the company to kind of design their study, and it would address the issues, I think, in terms of blood pressure and renal toxicity, and that sort of thing.

DR. PETRI: I believe Dr. Torley had a comment.

DR. TORLEY: I was just going to comment that to the combination study, there was an open-label extension that

took a very small number of patients out to a total of two years. That was only 21 patients. In terms of a year, approximately 100 patients were treated for the duration of one whole year, but that is the total exposure combination that we formally studied.

DR. PETRI: Dr. Chambers.

DR. CHAMBERS: As you continue to discuss this, I would like to hear some kind of notion of what you are talking about, defining long term and defining what kind of incidence you are looking for.

DR. PETRI: Dr. Simon.

DR. SIMON: I think that what Dan just alluded to would be a Phase IV specific trial looking at probably a two-year evaluation of the combination therapy. In addition, I had actually thought that there also should be some registry that is required where patients would be followed over time regardless of what they were on.

So, I think that we are really talking about two different issues, and in a Phase IV trial, I would be very interested in knowing about liver function, pulmonary function, kidney function, blood pressure, and some issues of --

DR. PETRI: Lipids.

DR. SIMON: -- lipids, and cardiovascular death, and

some issues regarding metabolism of the drug, both drugs under the circumstances.

DR. JOHNSON: How many patients would you want?

DR. SIMON: Thank you. David, power, what is the power calculation for this?

DR. FELSON: I actually think there is two different studies here that we ought to recommend, and I think we have talked about them sort of off and on. One is a cancer study which could be linked with some kind of SEER registry of cancer cases, which is different from the more intensive personal evaluation study we are talking about when Lee just talked.

I think the other one is one that Lee and Michelle have sort of been talking, which could be sort of operationalized as a longitudinal follow-up study of people treated with cyclosporine for a while to find in some reasonable way, some of whom are co-treated with methotrexate, which I think is going to naturally occur, and I don't think it has to be prespecified.

What we are interested in here and what we have been talking about all day is all of the potential side effects of cyclosporine that may be long term, and after all, this is a discussion of cyclosporine, and not methotrexate.

I think a peripheral concern is that cyclosporine may

elevate and increase the toxicity of methotrexate, which could be addressed as part of this study. The cyclosporine follow-up study would last for years, and I actually think five years is a little bit on the short side.

I think many of the side effects we are talking about, for methotrexate, if you think of the example of methotrexate in liver disease, it has taken us 10 years in small samples to figure out that, you know, perhaps what is going on perhaps we still don't know, and I would think that that kind of cohort study is a reasonable idea here, that we want to get data on rough incidence over time of renal insufficiency defined in a particular way, some idea of the curve of cholesterol over time, some of the blood pressure changes that occur chronically in long-term treated patients.

I think all of those are reasonable. I don't think they are overwhelming, I don't think we are talking about -- for the longitudinal study I don't think we are talking about thousands of patients, because I think all we are interested in is elevated, substantially elevated occurrences compared to a normal RA population, and substantially elevated would have to be operationalized, but might be reasonably done in a couple of hundred patients, you know, followed over time to see if there is a marked

increase in renal problems, if there is a marked increase in blood pressure problems, et cetera.

You know, to study 1,000 patients, number one, it becomes very difficult to do, and number two, will then give you power to detect modest changes, and we are happy to know about modest changes, but what we are really concerned about here is that these people are all going to get renal insufficiency in five years or 10 years, and we want to know that.

DR. PETRI: Dr. Miller.

DR. MILLER: The FDA paid me to come up here and paid me to serve as a consultant to the committee. I haven't said very much today, but before you make this recommendation, you need to think about several things.

Number one is on page 6 and 7, and you need to go back and review your logic one on one from college, because the barn door is still open. You do not have a measure of whether or not there is an interaction, and as a matter of fact, as long as you use designs that use "arms," you are not going to get one.

Now, if you are going to sit there and tell me you have got evidence on the short term, when you don't, and you are about to ask the sponsor to make the same mistake for the next five years, you are really -- you have got a problem,

folks, and you had better get your own, your company statisticians, your FDA statisticians together and find out how you are going to quantify that interaction because you cannot do it with this series of experiments from 651 to 2008. It can't be done.

All you have got to do is just calculate the expected value of those outcomes and it just don't work, and so I felt compelled to say that. Tomorrow, I will say quite a bit more about these designs.

DR. PETRI: Dr. Chambers.

DR. CHAMBERS: I think we have heard, and I am sure the sponsor has heard, the types of information we are looking for long term. The question is I mean we are talking about potentially very long treatment periods, is five years sufficient for what we expect to pick up, and what type of incidence rates are we trying to narrow things down to. Do we want to pick things up within 10 percent rate of things happening? Do we want a 1 percent rate? Do you want it at a 0.1 percent rate?

We will work out with the numbers of patients that means and the dropouts and followups, but just give me a ballpark of what type of certainty you want to have that we don't have these events.

DR. PETRI: Dr. Felson.

DR. FELSON: I don't know. I mean this would require some kind of reasonable consensus of what a clinically important increase in renal insufficiency is compared to control untreated patients, and I am not sure off the top of my head.

I might bow to Andy here to make a suggestion as to what a reasonable clinically important increase in the cumulative incidence of renal insufficiency defined in a particular way would be, that I would think we would want to know and how precisely we want to make that estimate I guess is the concern.

That would be certainly one outcome, and another would be blood pressure. I guess that is a continuous measure, so one could just measure blood pressures in these people over time. The renal insufficiency issue I think is the more critical one.

DR. PETRI: Let's add hepatic fibrosis there, though.

DR. FELSON: Well, that is for the methotrexate treated.

DR. PETRI: Yes, we are talking about follow-up of the combination-treated patients.

DR. WHELTON: There are available data to tell you that if you go from untreated to treated, that there will be a 30 percent on average detection of renal impairment or change

in renal function by the definition of what we heard this morning in 30 percent of such individuals after six weeks, 12 weeks, whatever the exact figure was.

Similarly, we were told that that was an increase of 11 percent approximately in systolic and in diastolic blood pressure change to make it such that those individuals became hypertensive.

So, those are pretty big numbers going from baseline. I think when it comes to the issue of neoplasia, it becomes far more complex and much more along the lines of what you have suggested, the care and the thought and the numbers, but I do not think you would need a very large cohort to get a handle on the issue of renal impairment and hypertension.

DR. LIANG: Actually, just speaking for myself and no one else, I really don't care about things that are reversible or treatable. I mean hypertension is fairly easily dealt with, I think. I am really more interested in permanent scar to the kidney and cancer in terms of things that I would have to tell my patients to deal with.

DR. FELSON: I was actually thinking exactly what Matt said, that maybe talking about this makes it clearer exactly what we are interested in. I think what we are interested in here is irreversible changes in creatinine including in patients who have discontinued the therapy.

What we don't know about from these short-term trials is how long one needs to treat patients before one begins to get into this problem and whether long-term treatment, which is naturally going to occur once this drug begins to be used more widely, okay, increases the risk of irreversible changes.

So, I think it would be helpful to identify a cohort on treatment, some of whom stop treatment and need to be followed for creatinine changes, who have been treated for varying periods of time and others whom remain on treatment.

DR. LIANG: But it sounds like on your open-label experience that most of the people don't stay on this. Is that the 21 remaining and are still standing at the end of 24 months that we saw?

DR. TORLEY: There were a fair number of patients who discontinued that study because they could not be maintained with a serum creatinine less than 30 percent. There were also patients who elected not to continue, and the Canadian center dropped out of the second year. So, some of them were adverse events, others were just administrative.

DR. LIANG: Right. This is our experience with other DMARDs. I think that when you said what year, what's the milestone, I mean obviously we want the longest data possible, but I think you are going to get some kind of

median duration of a couple years before someone flunks or gets some side effects.

DR. PETRI: Dr. Simon.

DR. SIMON: Matt, at the risk of belaboring this, I would like to suggest that I would agree with you, anything that is reversible and eminently treatable I am not as interested in, however, taking a patient with normal kidney function, having them go onto this drug, have them develop high blood pressure, which is probably not divorced from renal damage, and knowing that when they go off of the cyclosporine, they have sustainable hypertension that needs to be treated thus forever based on the use of the drug, doesn't make it reversible and makes me very worried about it, and thus, as a result, I would not minimize the evidence that could be accrued by watching the blood pressure changes, as well. So, that would be my argument about that.

DR. JOHNSON: Do you think that you would have to formally de-challenge patients?

DR. LIANG: Yes. I think you would have to.

DR. SIMON: I think you would have no choice. As a Phase IV trial.

DR. JOHNSON: I thought David was implying that maybe you could get around that.

DR. FELSON: I personally think you are going to have

naturally de-challenged patients, and I think you can follow their renal status and their blood pressure, and that will help you. You are sort of talking about doing a withdrawal trial and look for side effects, and I am not sure that is necessary.

DR. LOVELL: I think valuable data could be gleaned from both groups, the ones that don't withdraw and are still on the drug at five years in addition to those ones who do withdraw for whatever reason, and find out whether the changes seen are irreversible or reversible. So, I think there is information to be gained from both, and I would be opposed to imposing a withdrawal arm with the study.

DR. PETRI: We would like to take a 15-minute break. When we reconvene, we will be talking about the Pediatric Rule.

[Recess.]

DR. PETRI: I would like to invite all of the pediatric rheumatologists and other pediatricians in the audience to feel very comfortable coming to the microphones to participate in the discussing this afternoon.

We thought it was very important to start with an actual definition of the Pediatric Rule because many members of the committee are not familiar with this rule, so I would like to start by asking Lisa Rider if she could address this

for us.

Pediatric Rule

DR. RIDER: In order to facilitate labeling of agents for use in pediatric populations, the Agency adopted the pediatric use label regulation in December 1994. The labeling regulation states that when the course of the disease and the drug's effects are sufficiently similar in the pediatric and adult populations, to permit extrapolation from the adult efficacy data. Then, pharmacokinetic, pharmacodynamic and safety studies are required for pediatric labeling of the agent.

This regulation applies to all new applications to the Agency, as well as retroactive applications and currently labeled products.

DR. PETRI: Are there any questions or discussions?

DR. RIDER: I am going to present one more thing. In the Rheumatology Working Group's proposal for the application of the Pediatric Rule to JRA, which is in the Draft RA Guidance document -- and we will discuss this further tomorrow -- the Pediatric Rule would be applied to the signs and symptoms claim only. Also, the extrapolation of adult RA efficacy data would be to polyarticular JRA only, and this would be only if it is biologically plausible that the agent would have a similar effect in JRA as in

adult RA.

As with other applications of the Pediatric Rule to other pediatric populations, we still need pediatric dosing and safety evaluations in polyarticular JRA patients in order to obtain a label for polyarticular JRA.

DR. PETRI: Are there questions about the Pediatric Rule? Dr. Lovell.

DR. LOVELL: It is more apparent what might be entailed in a pediatric dosing type study, PK/PD data, but what did the division have in mind when they talked about safety evaluations in terms of numbers of patients, and that sort of thing?

DR. RIDER: This is going to undergo further discussion tomorrow. Generally, we would anticipate that for most agents, that the studies are going to be relatively small to establish dosing and some safety, but that there may be a great need for post-marketing surveillance given the small numbers of pre-marketing license patients studied.

DR. CHAMBERS: There is no predefined number or predefined study design or link to follow-up, so it is that type of issue that we would hope to get comments for something like cyclosporine from you today, or tomorrow, in general guidance.

DR. PETRI: Is there additional discussion about the

Pediatric Rule?

We are going to be turning to the sponsor's presentation. Dr. Perry wanted to make some initial comments.

Sponsor Presentation - Pediatric Data

Introduction

DR. PERRY: Good afternoon. Mike Perry, Vice President of Regulatory Affairs, Novartis.

[Slide.]

Issue 3 proposed by the FDA for consideration by the committee is presented on this slide. It poses the following question: What additional data, if any, would be needed in JRA to permit the labeling for polyarticular JRA via the Pediatric Rule?

It is critical for the committee to note that Novartis has been specifically requested by FDA to present available data on the use of cyclosporine in JRA, and kindly recognize that these data are not part of our NDA database of clinical trial experience, but are a rather modest compilation of data derived largely from case reports and abstracts.

[Slide.]

I don't think I need to go through the next slide. I should have coordinated it with Dr. Rider. Thank you.

[Slide.]

I guess without further ado, with that as background, I would like to introduce Dr. Vibeke Strand, Clinical Association Professor, Division of Immunology, Stanford University School of Medicine, who will present an overview of these data for the committee.

Summary of Data

DR. STRAND: Thank you, Mike.

I would like to start by saying that I am not a pediatric rheumatologist, although I have treated some cases of JRA in my past life as a practicing rheumatologist, and I still do consult and see patients at Stanford Clinic.

I was asked to survey the literature and prepare a summary of that the available data was for the use of cyclosporine in juvenile rheumatoid arthritis, and that is what I am going to show you.

There are some formal PK data from the pediatric renal transplant population which is in the Neoral NDA for transplantation and which I will refer to.

[Slide.]

As many of you know, the estimated incidence of juvenile rheumatoid arthritis is probably 10 to 20 per 100,000 and the prevalence is somewhere between 30- to 50,000 cases in the United States and therefore a rather limited clinical indication.

Polyarticular accounts for approximately 30 percent with that type of onset although many of them may change over time. It has a moderate prognosis which is generally believed to be which is generally believed to be worse in the rheumatoid factor-positive population.

Pauciarticular onset is probably two-thirds of the patient population in onset and has an excellent prognosis if the patients remain with pauciarticular involvement, but again if they become polyarticular, they tend to have a worse prognosis.

Systemic onset is the minority of patients with a moderate prognosis, but as many as half of them develop the chronic destructive arthritis that is characterized by polyarticular course.

Treatment includes the usual antirheumatic therapies, some of which are not specifically labeled for in juvenile rheumatoid arthritis.

[Slide.]

The initial positive case report of cyclosporine in systemic juvenile rheumatoid arthritis was in 1986. Since that time, there have been published open-label series, usually iterative abstracts which update the number of patients, and for some it is difficult to ascertain how many of the same patients have been described in each abstract,

but those are included in your book and you can refer back to them.

In total, approximately 95 patients with JRA have been reported treated with cyclosporine, 60 with systemic onset disease, 17 with polyarticular onset disease, 4 with pauciarticular, and 14 unspecified.

In addition, there are case reports of 7 patients with adult Still's disease being successfully treated with cyclosporine and most recently 8 cases of macrophage activation syndrome, which is usually a fatal complication of JRA, have been benefitted by the treatment of cyclosporine, 7 of whom had systemic JRA as background.

In general, the mean peak dosage has been 5 mg/kg/day in the studies from 1991 to 1996, and I am going to review them after this next summary slide.

[Slide.]

Essentially, one can ascertain from these reports that cyclosporine appears to be efficacious in refractory disease, in other words, patients who failed all other available treatments, clinical improvement in signs and symptoms, which include fever, arthritis, as well as decrease in sed rate or CRP, have been reported in somewhere between a quarter to three-quarters of the series; a decrease or discontinuation of concomitant steroid therapy

has been accomplished in as many as half to all of the patient population, and remissions have been reported, which have been both drug dependent and drug independent in some of these patients.

In general, the adverse events that have been reported seem to be similar to those that you have heard about today in adult RA, specifically, there have not been new reports of other types of adverse events.

Elevations in serum creatinine, hypertrichosis, hypertension, gum hyperplasia, GI complaints, infection, anemia, and thrombocytopenia account for most of the reports. Most of these have been reversible with a decrease in dose or discontinuation of cyclosporine therapy.

[Slide.]

The first series of patients was published from Oslo, included 10 systemic and 4 polyarticular. This was open-label treatment and this was quite a few years ago, and so therefore the doses were as high as 15 mg/kg/day. These were patients with refractory disease. They were ages 5 to 18 years in age, and generally had a disease duration of 6 1/2 years. Fourteen of them had already failed methotrexate and 11 had failed azathioprine and other cytotoxics.

The majority were treated for longer than 12 months, 11 withdrew: due to lack of efficacy in 4 and adverse events

in 7. Anemia and increased creatinine were reported, and this was felt to be due to the high doses, and recommendation was that doses be less than or equal to 5 mg/kg/day.

[Slide.]

The largest series of JRA patients has been reported over time from Milan in Fantini and Associates, and the most recent abstract was the last ACR meeting in October.

It includes 38 patients -- and we are not counting trice here because there are enough abstracts to actually sort it all out -- 33 with systemic disease, 3 pauciarticular, and 2 polyarticular JRA. All of it has been open-label treatment.

The mean peak cyclosporine dose was 4.6 mg/kg/day, but the maintenance dose was more like what has been reported in the adult series of 3.5 mg/kg/day with a range of 1 to 6.

Remission was reported in 6, improvement in fever in 26 of 29, improvement in arthritis in 18 of 32. The steroid dose was decreased in 17 and discontinued in 6 of these 17.

Twenty-eight patients ultimately of the 38 withdrew over time either due to lack of efficacy or flare, which I consider to be one and the same thing, disease progression despite treatment occurred in 7, and adverse events occurred in 7, and were reported to be increased creatinine ,

hypertension, and decreased platelet counts, which necessitated withdrawal.

The other adverse events again looked to be like the adult population. The opportunistic infections of three here were not characterized in any of the abstracts, but the others are pretty similar.

The conclusions from these series were that this drug is beneficial in refractory disease and can be steroid-sparing, that remissions have been reported in as many as 17 percent, 9 patients remain on treatment, successfully controlled, for two months to nine years, and the adverse events appeared to be dose-dependent and reversible with adjustment of dose or withdrawal of drug.

[Slide.]

The other fairly large series comes from Genoa, 13 JRA patients, again predominantly systemic. The mean peak cyclosporine dose was 5 mg/kg/day, but many of the patients were maintained on 3.5 mg/kg/day.

The age range here was 7 to 16 years, and the disease duration was 6 years, so again we are looking at refractory disease unresponsive to conventional therapy. This group reported remissions in the majority of patients, but that they were drug-dependent, they showed decreases in the joint counts in 3 of 13, a decrease steroid dose to more than 50

percent of baseline in 4 of 9, and normalization of systemic symptoms within a month.

However, as I said, they felt that these were drug-dependent remissions and that 6 of the 10 relapsed after withdrawal of therapy. They did not see increased creatinine in this patient population. They did see hypertension, hypertrichosis, alopecia, and polyserositis, edema, and decreased protein in a small number of patients in the total series.

Their conclusion, that it was beneficial, steroid-sparing again, but that the remissions were drug-dependent.

[Slide.]

Finally, a small series in Los Angeles with 11 patients, 7 of whom had JRA and 4 of whom had polymyositis, dermatomyositis. Again, improvement. Steroid dose was decreased in all patients with JRA. GFR was elevated in half of the series, and it is not clear how many of these were the JRA and how many of them were the dermatomyositis, but it was a decrease of 25 percent maximum. Mean dose was between 3 and 5 mg/kg/day.

In the Moscow series, of which there are actually two abstracts, they described out of 15 patients, most were polyarticular in this case, a very good response in

two-thirds, a good response in one-third. The mean dosage was 3.5 mg/kg/day, and these adverse events again look rather similar to the adult population.

[Slide.]

So that in summary is the published data in juvenile rheumatoid arthritis. In terms of pharmacokinetics, I expected that we were going to talk about the pharmacokinetics of Neoral versus cyclosporine before this. I am standing on a piece of tape that keeps sticking to the heel of my shoe, so I can't move, forgive me. I guess somebody wants to keep me here.

In general, when one is switched from Sandimmune to Neoral because of a certain population of patients having less good absorption of cyclosporine, there is more effective absorption of Neoral and the relative AUC is therefore increased or the relative bioavailability is increased.

In the group of adult renal transplant patients, and this is, as I said before, from the Neoral NDA, 55 patients with an age range of 50.8 years, there was a 31 percent increase in relative bioavailability when they were switched from Sandimmune to Neoral.

If we look at Study N105 that is contained in this same NDA, there is data on 12 pediatric renal transplant patients

ages 4 to 11, and 18, ages 12 to 18. Again, one sees an increase in the relative bioavailability of approximately the same magnitude, which is to say that that is roughly the understanding of the difference in PK in the pediatric population stable renal transplants.

[Slide.]

What is available in JRA is one, a single case report from Goteborg, Sweden, of three patients with JRA ages 5 to 19. Obviously, this is quite limited, but two of these patients on changing from Sandimmune to Neoral had an increase in the Cmax, and this would suggest that they had been poor absorbers of cyclosporine. A third patient had stable levels between the change of Sandimmune to Neoral.

Just to show the relative range of a percentage increase in Cmax, this is not unlike what was seen in Study N105, which I showed to you on the previous slide, and what has also been reported in stable renal transplant and dialysis patients ages 11 to 14, and stable liver transplant patients, which tend to have a bigger difference between Sandimmune and Neoral bioavailability ages 2 to 16.

[Slide.]

In summary, in the context of the Pediatric Rule, it could be argued that based on the efficacy in adult RA, this drug would be expected to be beneficial in polyarticular JRA

and more particularly rheumatoid factor-positive polyarticular JRA.

The reported series that I have reviewed, although limited, appear to show benefit in refractory systemic onset JRA, and I know that as many as 50 percent of these develop a polyarticular disease.

The literature supports the biologic plausibility of the use of this agent in the treatment of polyarticular JRA, but the data are limited.

Thank you.

DR. PETRI: Are there questions for Dr. Strand?

We have added pediatric rheumatologists to our committee, and I think one very good way to start this discussion is to ask them for their own personal experience with this drug.

Discussion and Question 3

DR. LOVELL: I would ask this of people from the company. What concerns do you have generalizing from renal/liver transplant data in children to JRA patients? I would like that information from someone who has more experience with these drugs than I do.

DR. CHOC: Could you restate that question again?

DR. LOVELL: Well, in the adult, we had the luxury of looking at transition or conversion data for PK and PD from

adult RA patients from Sandimmune to Neoral, but in the children, we are left with trying to generalize from transplant patients to JRA patients, and I was wondering if you could talk about what the pitfalls or strengths might be there.

DR. CHOC: Well, we do have the Vibeke slide showed a comparison of adult renal transplant data to pediatric renal transplant data. We also do have some information on liver transplantation, and when one looks at the comparison of pediatric, the relative bioavailability of Neoral and Sandimmune in liver transplantation in pediatric patients compared to renal transplant in pediatric patients, the differences there are similar.

Now, again, albeit there are still two different transplant populations, but with respect to -- well, I guess that is about the only way we can address the comparison of pediatric data. I mean the limited data that we had from the JRA patients was just -- all that was available was differences in Cmax, and so we tried show with that other slide that the difference in Cmax in those few patients that were observed were in the same range that we do observe in other pediatric populations.

DR. STRAND: I think the only other thing you could say -- and I don't want to be trying to read too much into the

data -- but one in general agrees that systemic JRA patients are a sicker population than the polyarticular ones in general, and one can say also that the liver transplant patients are the ones that have the more problematic absorption of cyclosporine, so in fact seen that there is more similarities and differences between the renal and liver transplant would be some confidence that the systematic JRA patients would be accounted for in both of those patients populations, as well as the polyarticulars.

DR. PETRI: If I could start to call on our pediatric rheumatologists for their experience with this drug. I see you pointing at each other. Dr. Lovell, do you want to start?

DR. LOVELL: From my own personal experience? My own personal experience is limited to one patient, because I haven't in our group treatment approach to this problem with methotrexate failures, on standard dose methotrexate, what we have done is to actually force the dose of methotrexate as high as 1 mg/kg/week.

So, we are all forced, all pediatric rheumatologists are forced to try things that haven't been proven in patients who are methotrexate failures, and some physicians have taken the route of forcing methotrexate beyond its usual recommendations. Others have taken the route of

looking at cyclosporine.

I can tell you that the experience with forcing methotrexate doses very high has been that it is only of moderate benefit, so there are still patients who are significant methotrexate failures, and still have very active destructive disease on as high as 1 mg/kg/week. So there is a need for another agent in some of these patients over and above even very high doses of methotrexate.

It is just that I personally haven't utilized cyclosporine. So, if you are limiting my remarks to my own personal experience, it is one patient.

DR. PETRI: I don't want you to feel that we are limiting just to your own experience, but your knowledge of the field. Let me ask Dr. Barron if she would like to comment, as well.

DR. BARRON: My experience has been similar to Dan's, that I personally have not treated a JRA patient with cyclosporine, but I am aware of the other pediatric rheumatologists' experience in the country.

Some of my concern is that the systemic JRA patients are certainly different than the polyarticular patients, and you are often treating different aspects of the disease, and most of the studies have included primarily systemic JRA patients.

So, it is a little confusing in how you are going to extrapolate that data to that polyarticular JRA patients, but I think that most people in the country, as Dan has said, have pushed the methotrexate first, and I agree that we need another agent, because not everybody responds to that medication.

DR. PETRI: Dr. White.

DR. WHITE: I have had experience with about five patients and have done what everybody else does and push methotrexate. When I have added cyclosporine, I have actually dropped the methotrexate dose. I have not had the guts to have 1 mg/kg of methotrexate plus cyclosporine.

But I do think that the issue of the different groups of JRA, we will talk about this a little bit tomorrow, they may be slightly different diseases, so we are trying to force them into known categories here. I think you have to be very careful.

I think the seropositive, which is where I have tried it, in a young, seropositive polyarticular onset and course, that is where I have used it, I haven't had the guts to use it in a systemic disease because of these very funny events that can occur whether it is sulfasalazine, gold, or whatever, I haven't had to do that.

So, I am sort of echoing what other people have said.

DR. SILVERMAN: Earl Silverman from Toronto for Sick Children. If I may talk a little bit, two things. One, as people know me, I have advocated against some of these drugs in systemic JRA. Looking at the JRA rule here, possibility of mechanism of action is actually appealing, both the preliminary data and the macrophage activation syndrome, as well as the mechanism of action that it actually may be safer in systemic JRA than some of the other drugs we have used.

Our experience has been again, as everybody else does, you push the drug you know. You push it until it doesn't work. You hit 1 mg and it doesn't work. We have treated in our center I don't know somewhere between 5 and 10 patients with cyclosporine of either polyarticular or systemic, so we have had some experience in both.

The safety profile looks okay. We have not run into any toxicity, to be honest. When the creatinine has gone up, we have dropped the dose, and it has come back down, not I think irreversible. The efficacy is obviously only in patients who failed very, very high dose of methotrexate, so I just want to echo what both Karyl and Dan said, is that there is no other drug on the market right now aside from methotrexate that appears to work in JRA, and other drugs are needed.

That is really the emphasis. When we have a drug like cyclosporine or other second-line agents that are plausible -- and I think that is what the JRA rules says -- the studies have to be done, and we have to look at what is available.

In addressing this particular drug, I think the safety is what exists in the transplant data. I think we know the profile. The bioavailability, limited as it is, looks similar to the bioavailability that is given in the transplants. Applying the JRA rule may be reasonable.

So far the patients treated certainly in North America from what you have heard from everybody else are only the ones who have failed, not even high dose, but what we call super dose of methotrexate, and that would be the experience I guess.

The other experience people do have on the safety, however, and certainly our center has it also, is in dermatomyositis. Again, the safety profile looks fairly good.

DR. LOVELL: I think there are some unique aspects of the pediatric database. One is that cyclosporine is oftentimes used as a rescue drug for patients who have had life-threatening toxicity from more standard JRA therapies such as sulfasalazine, methotrexate, and gold shots.

The macrophage activation syndrome is oftentimes provoked in JRA patients by the use of one of these three drugs, and in those instances, cyclosporine has been a lifesaving therapy for those patients.

Two, the patients that have been in the database, that have been treated with cyclosporine, most of them have been on very high doses of prednisone, 1 to 2 mg/kg/day and still have active severe disease, the end primary end point for those trials was steroid tapering, which you do at the risk of worsening your joint counts, because if you decrease the prednisone from 2 mg a day down to 0.5, then, the consequence of that is that your joint counts and other articular parameters may not be accurate indicators of the drug effect because you have confounded the finding significantly during the course of study by tapering the steroids, but the dose of steroids is so high and such a problem in children that that becomes the primary end point, and cyclosporine in the trials in which it has been used has been a significant benefit in steroid tapering, and not just marginal tapering, but big time tapering from 1 to 2 per kilo down to off or tolerable doses.

The other point I want to make is that the effect of the drug is really quite dramatic in many patients with almost immediate, like within one to two days resolution of

fever and rash and systemic malaise, and the other point is that in one of the trials, they had what they called drug-induced flares of the disease, which I would take as reassuring in that the cyclosporine was, in fact, doing something.

You know, there is a spontaneous remission rate in JRA that is higher than in adult RA, and if you taper the drug and the remission persists, you wonder whether it is spontaneous or whether the drug did it. The fact that there is a very high percentage of flares after you taper the drug suggests to me that cyclosporine was doing something, so I take that as somewhat reassuring data rather than kind of punitive data towards the drug.

DR. PETRI: Dr. Felson.

DR. FELSON: Can I ask someone who is knowledgeable about the pediatric transplantation literature what the long-term effects of cyclosporine in kids have been, has this been studied, are there data on long-term renal effects and some of the other side effects we were talking about?

DR. LOVELL: Neoplasia.

DR. FELSON: Yes, including, yes, neoplasia would be nice to know about, too.

DR. TORLEY: Unfortunately, our renal consultants who would have experience, particularly Dr. Appel, had to leave,

so there is nobody here that can address that.

DR. STRAND: We could still say one more thing. I just wanted to point out that the patients that were included in the NDA, there is six-month safety data on those 30 patients, so that is available, as well.

DR. CURTIS: We deal primarily with adult transplant patients, but the pediatric transplant experience has been one where the dose of cyclosporine seems to need to be greater than in the adult, and they seem to tolerate the drug better than the adults in terms of less toxicity.

There is not to my knowledge in the transplant literature any evidence of renal insufficiency developing to end stage from cyclosporine, and I am not aware of any increased neoplasia above what was seen with azathioprine.

DR. PETRI: Dr. Simon.

DR. SIMON: Again, I wonder if there is any data about growth or given the fact that inflammatory disease sometimes changes growth patterns, do you return back to a better growth pattern, is there any evidence or data about manipulation of calcium, phosphorus, magnesium, any changes in bone, do we know anything about that in children?

DR. LOVELL: Not as it relates specifically to cyclosporine, at least in JRA patients, although with the caveat that if one is able to significantly control the

inflammatory process, and steroid taper, then, the effect on bone and growth would expect to be much in the positive, but at least in the JRA series, I don't know of any real data to that effect.

DR. SIMON: Because that raises the issue again of risk/benefit as it relates to sustaining a transplant, which you might sacrifice certain risks for the benefit of maintaining that as opposed to JRA, which may not be exactly the same circumstance.

DR. LOVELL: My own experience with bone mineralization in JRA is that in JRA patients not treated with steroids, but treated with NSAIDs and methotrexate, that in the prepubertal population, about 30 percent of them have significantly low bone mineralization as measured by dexascan, and that in the adolescent population, in other people's studies, the percentage has actually gotten higher, over 30 percent.

What seems to be most significantly associated with that decreased mineralization is the degree of articular inflammation over the above dietary intake or activity, that sort of thing.

So, any drug that would decrease the long-term inflammation in the joints would seem to potentially weigh in the positive in terms of risk/benefit.

DR. PETRI: Dr. White.

DR. WHITE: We are talking about patients that are on very high-dose corticosteroids that, by the nature of those drugs, wreck their growth and a lot of their bone parameters, so the fact that this drug showed you could taper prednisone actually may be a tremendous benefit, because we use awfully high doses as you saw, 2 mg/kg/day is that of drug, and the toxicity there is very high.

DR. LOVELL: In terms of growth, we have a long-term study of JRA patients followed into adulthood, and 50 percent of the systemic JRA's adult height was below the 5th percentile. Now, this was a study that was pre-methotrexate, so that the outcome might be better with methotrexate, but the effect on growth and about a 25 to 30 percent of the polys were below the 5th percentile, so that was a significant shift to the left in adult height in these JRA patients in these earlier studies.

Our hope is that with methotrexate or other steroid-sparing drugs, we can decrease that, but the potential for growth inhibition in JRA patients is very high given the use of steroid and that sort of thing.

DR. PETRI: Dr. Liang.

DR. LIANG: This is really fascinating, but I don't understand why we are discussing this, because this is a

rare condition, it's only people in academic health centers that would be using these things, and usually nervously. Why do we have to label this? I don't get the point of what we are doing.

DR. PETRI: Let me ask Dr. Chambers to address it.

DR. CHAMBERS: We are discussing this because if it is a good drug to be used in this population, it is the general feeling of the Agency that it should be labeled to do so, so that physicians know that that is the case.

There were a number of surveys that were done in the pediatric population to look at what drugs were available to treat various conditions, and it was thought to be, and demonstrated to be, a lack of a number of different agents to treat both common and unusual diseases.

DR. LIANG: When they have to and there is nothing else and their backs against the wall.

DR. PETRI: Are there reimbursement issues, though?

DR. LIANG: I don't know. I am actually just trying to figure out what is going on here.

DR. CHAMBERS: There are reimbursement issues, there are malpractice issues.

DR. WHITE: Legal and reimbursement issues. It would be very helpful for us to have drugs that we could use.

DR. PETRI: Let me read the question because I think

that will help to focus the discussion

Question No. 3 is what additional data, if any, would be needed in JRA to permit the labeling via the "pediatric rule" for polyarticular JRA.

I think I would like to start the discussion by asking why are we limiting this to polyarticular JRA, didn't we see data that it probably is going to be effective for systemic?

DR. JOHNSON: Let me clarify something. This is a difficult topic to discuss because it's really kind of a whole different format than an NDA call, is it effective, does it have an acceptable risk/benefit.

This maneuver on the part of the FDA is an attempt I think to try to satisfy what is perceived as a need in the pediatric community and it is a different standard. I mean I don't think there is a question about that, but it begins with the proposition that you have an extrapolatable disease, and that is how you come up with the seropositive polys, because the perception is that kids with seropositive polys have a disease that -- well, stronger for seropositive, but we are expanding it to all the polyarticulars, that it is biologically plausible if you have an agent that works in adult polys, that it should work in kid polys, therefore will cook up a label that reflects information vis-a-vis safety and PKA or that the additional

dimensions that might be needed might be some PK information or some safety information.

This drug is a little unusual because its major exposure is in systemics, as we have seen. So, it is more complicated, and if you decide that it is extrapolatable in polys, and then implicit in that is going to have to be some kind of equivalence between the handling of the drug in systemics versus polys in kids, we don't have any data that really support that with respect to this drug. Maybe there are with respect to other drugs, but the issue is what further information or is what you have -- I mean if you argue that what we have is not adequate, then, we would like to know what you think would be further indicated.

If you argue that what we do have is adequate, then, presumably there would be some way to describe dosing and safety in the label.

DR. PETRI: Dr. Lovell, could I ask you to start to address this? If you could also address the question of whether you think systemic should be part of the generalization here.

DR. LOVELL: Well, to get back to Matt's question, I think he has hit on the heart of the issue, is that when we, as pediatric rheumatologists, say we need another drug, what we need is another drug that has been shown to be effective

in this population, so it is not just somebody needs to invent a better mousetrap, it is really that the drugs that you all currently use, that have been shown to be efficacious or not efficacious, haven't been tested in children, and that is the real rub.

The Pediatric Rule is kind of a middle ground approach to that where it might encourage companies to come up with a few more studies in JRA patients. Now, as people have shown, over 90 percent of the study data for cyclosporine is in systemic onset JRA patients, almost all of whom had some polyarticular disease.

The reports from those, although limited, suggest that the effectiveness of cyclosporine is both the systemic features and for the articular features, and that is the way cyclosporine is generally used in the pediatric community, is in systemically active, systemic JRA patients.

The database as it exists is much less satisfying in trying to address the issue of if you are treating articular disease per se, what the efficacy is.

I think if the question were to read about what additional data is needed for systemics, it would be much easier to answer, and if it were for systemic JRA, I think the additional data that would be needed would be some limited PK and PD data to make sure that the absorption is

kind of similar to what it is in transplant patients and some very limited short-term data in terms of frequency of side effects, it also could get at some information about efficacy in arthritis per se.

I think that the biologic plausibility of using this on polyarticular JRA patients downloaded from adult RA patients is sufficiently satisfying that we could answer that question probably in the same sense, but with less certainty that we could with systemic JRA just because we have less open pediatric experience with polyarticular JRA.

DR. PETRI: Dr. Barron, do you want to continue the discussion?

DR. BARRON: I think Dan has read my mind. I don't think I have anything else to add.

DR. PETRI: Dr. White.

DR. WHITE: No. That is what I was saying earlier. I think the systemic onset JRA is a slightly different issue, and I agree that you need to do some studies to look at metabolism. I think that is going to be important in that particular group, but where I would use it is in precisely the other, in the polyarticular, more adult group.

DR. LOVELL: The problem with rheumatoid factor polyarticular JRA, it is really about 5 percent of the JRA population, so it really doesn't address much of our issues.

The other advantage to cyclosporine is it has been dosed on the mg/kg basis, which is exactly the way we do drugs in pediatrics, so that we are many steps ahead in terms of dosing information with this drug than we are with the usual drugs that we try to extrapolate from adult RA studies, which are just kind of absolute doses, not based on the body weight or size.

DR. PETRI: Dr. Silverman.

DR. SILVERMAN: I just want to reiterate what was said. I think there was something unique about this drug. I think the Pediatric Rule, as I have learned to interpret it with the help of people who wrote it, says when it is plausible, and there is certainly no reason -- the arguments given by other people I won't reiterate -- why polyarticular JRA resembles adult RA, and the reading of most labeling would say as polyarticular JRA resembles adult RA in many aspects, and has been indicated in that disease, therefore, it is likely this would work be a very reasonable indication from my non-FDA perspective.

The systemic issue maybe is a little bit different. I think the only caveat I would personally put on that is the data collection, and I don't know, these are abstracts, and that is my only caveat. I would like to see somebody having looked at it rigorously, I am not sure the company has or

hasn't. That would be my only caveat on to how the side effects are examined for the rigorousness of the testing.

If that met that, then, 60 patients is a large number of patients to study, at least for preliminary data and extrapolation, I think with PK data would be a very good drug to have potentially available.

Going back to Matt's question, I work at an academic center, and I was questioned -- you will like this one -- just two days ago on why I was giving a patient methotrexate for dermatomyositis by my pharmacist. This is an inpatient, and the reason is because it is not indicated.

So, I think those are very real issues at very large academic centers which I hope the FDA would at least help and also come into Canada.

DR. LOVELL: I think the only caveat for JRA as opposed to adults is that the second-line agents that we talked about before, D-pen, hydroxychloroquine, and auranofin have been shown to be inefficacious in JRA patients in a placebo-controlled trial, so that kind of path B that we talked about for adult RA patients would even more so be dubious for JRA patients, so that the only second-line agent that has been shown to be efficacious for JRA is methotrexate.

DR. PETRI: Let me ask Dr. Whelton if he could address

any special issues in terms of nephrotoxicity of cyclosporine in children, would this 30 percent creatinine rule work in kids?

DR. WHELTON: I think the issues are very similar except renal biopsy is a little bit more difficult to do since it is a smaller target, but I think the issues are indeed, I mean truly the issues are very similar. There is a question that was addressed this morning that the serum creatinine in the pediatric population at a starting level is going to be substantially lower and that is in a kid aged one or two years of age, a normal serum creatinine will be in the range of 0.4-0.5. So, the upper limit for that age range, that will move into an ostensible range of renal impairment for a comparable adult, that creatinine would be normal.

So, there is just the issue of correlation of serum creatinine with age, the commentary about the renal transplant, kids doing reasonably well, in fact, slightly better than adults is certainly of interest.

DR. PETRI: Dr. Chambers.

DR. CHAMBERS: I guess I would like to take us back one step as far as the Pediatric Rule, and that being if there is reason to believe that you need studies in the pediatric population for a particular indication, that is what you

should be asking for, that is what you should be recommending.

The idea within the Pediatric Rule was that there were many cases where people were asking for studies just for the sake of asking for studies, and it was possible to extrapolate from an adult condition to a pediatric condition because the conditions were not substantially different, and if you could go and do that, don't just ask for a study in pediatrics just for the sake of asking for it. Extrapolate when you can, when it made sense.

DR. LOVELL: I think the reality is in the subset which cyclosporine is used. It's at the point at which you have life-threatening disease, and it is difficult for me to imagine ability to do a rigorous study in that population.

So, I think we are looking for an indication for very limited severe set of JRA patients in whom the kind of studies that would answer the question of efficacy, for example, would be very difficult to do or impossible to do.

DR. JOHNSON: But, Dan, you have been part of these deliberations. It seems like the consensus is that you can't extrapolate to systemics, and you can only extrapolate to the polys, so we sort of have a logical divide here.

Whether you can do a small study and get an efficacy conclusion that holds water is also doubtful in my mind.

So, I do think you are stuck unless you can fancy a way to actually do a trial.

I mean there are trials done with patients with life-threatening diseases even in pediatric settings, but it wouldn't be easy. I think the question that we are trying to address is to whether simply the extrapolation to the polys is a reasonable proposal given this haphazard 100-patient database of safety experience, is the dosing well established, that is the other component of that.

DR. PETRI: Let's try to address just that specific question, is there enough available to extrapolate to polyarticular JRA. If I could ask the three pediatric rheumatologists on the panel, and Dr. Silverman, just to address that.

DR. BARRON: I think that if you look at the number of studies that were shown, there aren't very many patients that fit that category, however, if you use the Pediatric Rule and say that the polyarticular patients are most like the adult patients, then, there probably is some leeway there, but I don't think we have seen any evidence, or at least shown today, because of the number of patients that fit into that category.

DR. PETRI: Can you give us an idea how many patients you would like to see before you would feel comfortable that

you had efficacy data?

DR. WHITE: I think you have pointed out the dilemma. The patient numbers are in systemic. It's the one that we are most uncomfortable with in terms of the severity of the disease, so the numbers here from looking at the nice summary that was done, is you see most of the numbers are in systemics, and they actually did reasonably well.

So, we are just going to have to live with that and say that perhaps since we feel most comfortable extrapolating to polys -- and I am not only just doing the seropositives -- there is a bunch of polyarticular courses that even though they are rheumatoid factor-negative, have a very severe course, so I broaden that group.

DR. JOHNSON: I think we have broadened it, too.

DR. WHITE: So I guess, you know, I was being conservative. By looking at the numbers, it looks like we ought to be able to extrapolate into the systemics.

The only issue is, is system is a broad term. There are those that are still systemically ill and when you have fevers, that may be different in terms of pharmacokinetics, and so forth, of drugs versus those that have gone on to a polyarticular course which fit into that group we are already feeling comfortable with.

I think that is where the rub is. It is that that

broad term "systemic" includes different types that I, as a pediatric and adult rheumatologist, sit here and say, you know, I feel comfortable with that, that has a systemic onset, have a poly course. I don't have as much trouble as I do with somebody that has actively got systemic disease, which is this macrophage activations and all these kinds of other things that happen in that setting.

So, you know, we have had the experience with systemic, but the question is where was that experience.

DR. PETRI: Dr. Silverman.

DR. SILVERMAN: I think, if I can address your question, your question was are you comfortable with the dose, I think that is what one of your questions was, and the safety of that dose, then, the answer to that is yes, I think the safety at the dose that is recommended for up to 5 mg/kg appears to be safe in dermatomyositis and other autoimmune diseases.

When I speak to my colleagues in transplantation, it appears to be quite safe, and I think the points made by the nephrologists is as many other drugs are in children, on a per-kilo basis, children appear to need much higher drugs and methotrexate is a classic example of that particular statement.

Whether it works in systemics is another issue brought

up in systemic JRA when it is active, and it is an interesting conundrum, because what we are saying is that it appears to work best in the systemics, but maybe it will absorb it as well, so maybe the levels are lower, but the Pediatric Rule says polys are similar from adults to children, so we should use it.

DR. PETRI: There is a lack of logic here. That is what has bothered me. My first question was why are we limiting this to polyarticulars if most of the data is in systemics.

DR. SILVERMAN: Because if you read the rule, and I was there when it was brought up, was the biologic similarities between the two diseases. It is not extapolatable from adult RA to active systemic JRA, and that was the point, and one of the caveats not put into the --

DR. CHAMBERS: I would disagree with that. There is not an automatic rule when it is extrapable and when it's not. It is the subject of things like this advisory committee to decide when it is extrapable and when it is not, and if the feeling of consultants and advisers to the Agency and within the Agency that this is extrapable, we would do so.

DR. SILVERMAN: Then, I will rephrase what I just said. At that meeting, it was not obvious that it was directly

extrapolable in active systemics, whereas, I think the consensus was polys were.

One of the caveats that maybe could go into this is what Dr. White was saying, was that maybe inactive systemics -- and one could define how long one didn't have fever or rash, et cetera, for, and then make an extrapolation, but it is an interesting dichotomy here when we are saying the data suggest its efficacy, but I am not sure we have to go at efficacy, because we are not even addressing, the numbers are far too small.

I think if we address the simple question that I was trying to answer at the beginning, does it appear safe at the dose, and does the dose appear appropriate, I think we have that data, and I think maybe we do need some PK data in systemics to show they absorb it, et cetera, how it is metabolized, and we certainly need post-marketing surveillance and long-term studies, but my fear of any drug being used in systemics of this macrophage activation, this life-threatening disease, as put forth by Dan Lovell, in fact, is quieted down because, in fact, we use this drug for that particular reaction.

DR. LOVELL: I think there are very few polys that are in the database and almost all the systemics all had very severe active articular disease. There is maybe in the

Italian study maybe two patients that really had minimal articular disease and maximal systemic features, but the rest of the database has honest, awful polyarticular arthritis, and the efficacy of the drug for those patients is both in the system features and in the articular features. So if you look at arthritis as arthritis, I think we can develop a plausible explanation for approval of this drug.

I see systemics as really our worst case scenarios. The reason the data is not generalizable from polys to systemics generally is because systemics throw you a whole bunch more things to treat than polys do, but the fact that a drug is effective in systemics with significant articular involvement gives me support for the plausible explanation that it would be effective for arthritis.

DR. PETRI: I think Dr. Luthra had a comment.

DR. LUTHRA: I wanted to raise a few questions. Maybe it is my lack of knowledge of pediatric patients, but as I reviewed some of the data that is being presented, comments have been made that we know those should be up to 5 mg/kg, yet, the data here is 4 to 15 mg/kg/day in the Oslo study, a mean of 4.6 mg/kg/day in the Milan study, and then a mean of 5 mg, so obviously, there are patients that are getting a lot more than 5 mg.

Also, when we talk about that this is safe, I am having some difficulty again. In 14 patients in the Oslo study, 11 withdrew, 4 for lack of efficacy, 7 for adverse events. That is 50 percent side effects that we are noticing.

In the Milan study, again, 18 patients out of 38 had increased creatinines. Do you accept this level of toxicity as being okay?

DR. LOVELL: First of all, in the Oslo study, their goal was to maintain trough cyclosporine levels at 3- to 800 ng/ml, so they were shooting for a very, very high dose compared to the dose we more commonly use.

In the setting in the patients that we are talking about, I think are a very severe subset of these patients.

DR. LUTHRA: I recognize that, so what I am trying to think is that the dosages that are effective, are very high, and there is a lot of side effects that we are seeing, I mean I don't treat these kids, but I am asking, do you accept this level of toxicity as being okay?

DR. STRAND: I think there is a caveat to this conclusion. One is that the Oslo study was the first series, and then they, in fact, concluded to dose reduce. The second is the summaries that I have given you are the peak, the peak mean doses, when I presented it to you, in fact, the mean doses. The maintenance doses were less, they

were more in the range of 3.5 to 5.

The third thing is that these are mostly systemic patients who have a lot of systemic illness and tend to have LFT elevations, et cetera. We know that those are patients that might be more prone to have less effective absorption of cyclosporine.

So, from that point of view, if any of these studies had been done with Neoral, there might have been a better correlation with dose tolerability and reported benefit. In that context, I just showed you those three patients' data when they were switched from Sandimmune to Neoral, which being a very small n is only a suggestion, but I think that may be one caveat to what you are saying.

DR. PETRI: Dr. Tilley.

DR. TILLEY: I guess I am a little confused, and maybe I would like to ask Dr. Chambers to clarify. If we didn't have this document in front of us at all, would the question not be did the data we see this morning give us information that would allow us using the rule to extrapolate to the polyarticular juvenile patients?

I think that was the first question that we were being asked, and in a way I think these data are confusing us perhaps. Are we really supposed to be just using the adult data to answer this question? I guess that is what I would

like to know.

DR. CHAMBERS: I think we took it for granted that there were not adequate and well-controlled trials in pediatric patients, so that was not a particular option.

DR. TILLEY: Right.

DR. CHAMBERS: And because of the Pediatric Rule and basically the Agency's desire to try to press and have more drugs available in pediatric patients, we were looking for -- the Agency has committed to either at the time of approval or during development or afterward, to essentially push sponsors to either do studies or find ways to make these things available.

In that vein, we had decided to bring this up as a topic, both to see to what extent we could use all the information we have and if that was enough, then, we would potentially find a label to put on that product now; if that was not enough, to be able to give direction to the sponsor about what else needed to get done, so that we could arrive there. That is the basis for it.

DR. TILLEY: So, I guess if we were talking about polyarticulars, then, what we would have wanted to see was what specific data do we have in addition to the adult data on polyarticular patients then. We can't really separate those out very well here from what we have been given.

So, what we have available to us is the adult data and then this compilation of sort of a mixed bag.

DR. CHAMBERS: There have been comments in the past that the most likely thing that would be extrapable was the polyarticular. That doesn't mean that is necessarily the only thing or necessarily in this drug, but based on previous discussions, that is what was generally thought to be the most extrapable.

We are bringing it up to both ask that question and maybe for this drug that still is, maybe for this drug it could be wider, maybe there is a subset of the systemic. We are asking those questions.

DR. TILLEY: I guess I am wondering if we could answer it in pieces, like piece one would be if we only had the adult data, how would we answer that question, and then given the adult data plus what we saw, how would we answer that question. Maybe that would help us.

DR. PETRI: I think there are a few more comments first. Dr. Strand.

DR. STRAND: I just don't want to state the polyarticular patients are thrown in here for their efficacy, as well, so this is not simply that this 60 responded and the 14 did not. In fact, all of the abstracts indicate that the articular signs and symptoms have been

improved in at least a certain number of patients. So, it is not a separation of the two.

DR. TILLEY: I understand that. I guess that was the issue, though, the fact that we can't tell how many of the polyarticular really did respond versus how many didn't, and how many of the polyarticular had the side effects and how many didn't if we are trying to answer the polyarticular questions.

DR. JOHNSON: To answer the polyarticular the data would probably be negative. I mean that part would be straightforward. They just culled the literature and dug out whatever they could find.

DR. TILLEY: I understand that, but I guess all I am saying is the literature that we got didn't separate the two.

DR. JOHNSON: I know, but I think that is the nature of the literature right now.

DR. TILLEY: In terms of data, what seemed to me that would be helpful is step one, divide these up to at least let us see what happened to those two different subgroups of patients.

DR. JOHNSON: Can you divide them up?

DR. STRAND: That is not possible. If it were possible, I would have done it.

DR. JOHNSON: So, we don't know how many of the systemics had bad polyarticular disease also?

DR. STRAND: The nature of the reporting is such that you can't separate them, but each abstract, in fact, pointed out that the polyarticular symptoms in many occasions were improved, and led me to believe that it was of equal benefit in both subtypes.

DR. LOVELL: Actually, I agree with Vibeke that you can't separate out the effect of the systemics and the polys, but several of the abstracts reported on what proportion of their systemic populations had limited articular disease, and it was very small. I think in the Italian population, it was only two patients. In one of the Russian studies, they talked about one patient, that sort of thing, so it appeared from the data that the vast majority of the systemic JRA patients had significant articular involvement in addition to their systemic disease.

DR. PETRI: I actually would like to try to pin people down, so let me start with Dr. Lovell. Is there enough information present already today to allow the Pediatric Rule for polys?

DR. LOVELL: In my opinion, yes, if you limit the indication to patients who are methotrexate failures, and the reason is that I think I have a problem with the

Pediatric Rule if it allows us to extrapolate from adult efficacy data, drugs that are less efficacious than methotrexate because all the other second-line drugs that have been effective in adults weren't in children except for methotrexate. So, I think methotrexate for us definitely represents the gold standard.

So, if we are looking for a drug for polys that we would extrapolate to use before methotrexate, it would have to be at least as effective as methotrexate. If we are looking for a drug to use in methotrexate failures or partial responders, then, I think the adult data with cyclosporine would suggest that yes, it is applicable to use the Pediatric Rule for kind of as an additive drug to methotrexate.

DR. PETRI: What about for systemics?

DR. LOVELL: Again, it gets kind of fuzzy as to whether you could use the Pediatric Rule.

DR. PETRI: Well, we have been told by Dr. Chambers that we can, so it is not fuzzy anymore if this committee can.

DR. LOVELL: The group of systemics that have very severe systemic, actively systemic disease that is requiring the use of steroids, I think that we could write for an indication and use, you know, a dose of steroids above a

trial dose, say, steroid-dependent at 1 mg/kg/day or more, and still have an active systemic disease, then, I think it would be appropriate.

DR. PETRI: My final question for you is what additional studies are absolutely mandatory?

DR. LOVELL: I think some small studies to look at bioavailability and absorption in systemic JRA patients who have active systemic disease and which absorption and metabolism of drugs is different.

DR. PETRI: Dr. Barron, let me pin you down next. Can we invoke the Pediatric Rule here for polys?

DR. BARRON: I think this side of the table is in agreement.

DR. PETRI: Are you in agreement with systemics, as well?

DR. BARRON: We are in agreement with what was just stated. I mean the caveat here is that they failed methotrexate and they fail high-dose corticosteroids in those two settings, and I think that is really the crux here.

DR. PETRI: Failed both, because we just talked about methotrexate failures, but you want to scale both.

DR. BARRON: I am giving that blanket in the polys and the systemics. Systemic disease has systemic features, and

that has polyarticular component, and they may have, those with the poly, have systemic features or not. So what I am talking about is the polyarticular group. They may have been labeled as systemic onset, but now they are having a poly course without systemic features.

That falls under the polyarticular group, and they have to fail methotrexate. I think that is what we are talking about here. I am trying to clarify. The fuzzy area is those that have systemic onset and keep their systemic features. They have also have polyarticular disease, but the fact is that is a different disease and they can be sick, and those people can be failing 2 mg/kg of steroids. That is a lot of steroids to fail, so we just arbitrarily said 1 mg. I don't know, but it's a lot. I mean I think that is the key here.

DR. PETRI: I think the pediatric rheumatologists have reached a consensus. Now I would like to broaden this to everyone else. I think the adult rheumatologists have brought up the point that we had to have post-marketing surveillance of the kids, not just for the long-term renal implications, but the long-term malignancy implications and perhaps other things in terms of growth and development, but let me ask the adult rheumatologists their additional comments.

Dr. Felson.

DR. FELSON: Let me make an additional comment especially to Dan. I think if we use the Pediatric Rule as you said yourself, Dan, and we would now think that methotrexate, auranofin, d-penicillamine, and a variety of other drugs we have good data on, don't work in JRA other than methotrexate, do work in JRA because we would have had abstracts like this, these 20-some abstracts from the same group, Fantini, et al., in Italy, that suggests repeatedly reporting the same patients that there is terrific efficacy in an uncontrolled setting, in other words, we wouldn't have had good scientific data testing the efficacy of this drug in JRA, and it would have been brought into JRA, wouldn't have known whether it really worked or didn't.

Now, we can't sit here and apply the Pediatric Rule and come up with a sense that we probably ought to give some kind of tacit approval to the use of cyclosporine in JRA even in particular subsets of JRA, but I suspect that you guys are going to want to do a trial at some point, and I am wondering if we shouldn't take a step back and say -- I realize this to some degree violates the Pediatric Rule -- but after all, you are going to want to do a trial anyway because people are going to want to test it in pauciarticular disease, just like you have in methotrexate

and every other drug that has been tested well in JRA, so that you now know what works and doesn't work in JRA.

Here, we are about to allow for the approval of something, and we won't know. We won't know whether it really works, because all we have is 20 abstracts from the same group somewhere in Italy, and it has really never been actually tested that I can see. Maybe there is one uncontrolled set of small data from the States. Why not do a cooperative study here?

DR. PETRI: David, I don't think anyone disagrees that it would be wonderful to have a collaborative clinical trial.

DR. FELSON: I was speaking to the labeling issue although one could take a step back and say it might speak to the labeling issue. I think I am encouraging in the same way we encourage certain post-marketing surveillance after we thought about adult labeling that this is going to be a drug that is going to be now used in JRA, probably even thought of using pauciarticular JRA, and somebody ought to do a trial before it gets widely used.

DR. LOVELL: I agree, but in pediatric rheumatology, the indication and the ability to do trials are much more disparate than they are in adult RA. You can use an indication in adult RA as a carrot to get people to do all

kind of studies that they would never consider doing in pediatric rheumatology because there is no payback, there is no monetary reward for doing that.

So, we are always kind of the fifth wheel when it comes to negotiating with companies, so I agree with you that doing these studies would be wonderful, but I think in our considerations we need to keep the indication and the need for studies a little less tightly bound with JRA than we do with adult rheumatology.

DR. PETRI: Are there additional comments from the rest of the panel? Yes, Felix.

DR. FERNANDEZ-MADRID: I think I would agree with what Barbara said. I think we have a Pediatric Rule which I don't think really applies to systemic JRA in my book. Then, we have the set of data that we have analyzed that is, by all standards, limited, and I would agree that a controlled study would be necessary for me to understand this problem and to be comfortable with approval.

DR. PETRI: I sense that there is going to be some dissension on this, and I would like us to sort of come to a vote and with a recognition that the Agency can take whether or not the majority opinion rules or not.

I would like to allow the pediatric rheumatologists to actually vote with us as a group on this. I would like to

have the first vote being whether the Pediatric Rule could be invoked for polys.

All those who feel the answer is yes, please raise your hands.

[Show of hands.]

DR. PETRI: May I see now a show of hands of dissenters, and the issue is polys.

[Show of hands.]

DR. PETRI: Again, remember we accepted there would be some dissension.

The next vote would be for systemics, those who feel the Pediatric Rule can be invoked, please raise your hand.

DR. WHITE: You mean the systemics with active systemic features?

DR. PETRI: Yes.

DR. WHITE: All right.

DR. PETRI: Raise your hand if you feel the Pediatric Rule can be invoked for systemics.

[One hand raised.]

DR. PETRI: Those who dissent, please raise your hand.

[Show of hands.]

DR. PETRI: So that one definitely did not pass.

Now, was there anything else on that question that someone would like to bring to a vote? Dr. Simon.

DR. SIMON: I just have one question to ask the pediatric rheumatologists. It has been way too long since I have seen kids, so I really need to have some advice here, maybe not way too long, but it has been a long time.

It seems that glucocorticoid use in this particular disease is not particularly attractive, particularly how much you have to give and the side effects of it are quite devastating.

It seems to me that we have a potential drug here that might spare that. We don't know a lot about that drug. We have some data that whatever rule we want to invoke really is just an arbitrary statement here.

We recognize that the ability to do a clinical trial, either randomized controlled trial or some other form of trial is quite limited in this particular patient population for many, many different reasons, but it seems striking that the data we do have could be very important in very, very sick people.

It seems that we should remember that part of our job here is the risk/benefit issue, and even with what we know, we know that it is probably safer than long-term use of 2 mg/kg of glucocorticoids in treating that disease, and we have an obligation to recognize that regardless of the other data that does or doesn't exist.

Some of the data can be accomplished over the long term just following the patients in their use as opposed to doing a randomized clinical trial. So under those circumstances, although I would traditionally agree with David, although that is a surprise, I would traditionally agree with David about the need for randomized clinical trials, I do think this is a very unique situation, and there is a lot of data out there that we could apply under these circumstances, and we are faced with a very serious risk/benefit ratio.

DR. PETRI: We had a few brief loose ends from this morning about the labeling of Neoral. One that we forgot to reemphasize was this issue of grapefruit juice and any other nutritional issues that are going to be very important for patient education, but of course physician education, as well.

Dr. Abramson had some additional comments and concerns about the NSAID interaction.

DR. ABRAMSON: I am sorry, there was on page 2-18 of the indications, we really didn't look at that carefully I think, where it talks about the concomitant use of nonsteroidals drugs with cyclosporine, and were on 401 it says that cyclosporine may be used with nonsteroidal anti-inflammatory agents.

Then, in the final two lines on 4-10 and 4-11, it says

that the adverse event profile is 588 patients who took concomitant NSAIDs and 214 did not, were similar. I think based on the data this morning, there was evidence that the addition of NSAIDs in some of the studies raised the creatinine substantially in a higher percentage of the people. I remember a number of 34 percent going up versus 17 at a lower dose of cyclosporine.

So, I thought that some language here to say that NSAIDs may adversely creatinine needs to be part of this, if this is the only place that NSAIDs are addressed.

DR. PETRI: That is especially important since naproxen is now available OTC.

DR. TORLEY: Probably just for a point of clarification, and the wording isn't clear, I think this is specifically referring to the types of adverse events like nausea, headache, et cetera. It wasn't specifically referring to creatinine, and we certainly can look at that.

The data I presented to you did show a greater incidence of greater than 30 percent increases. I can't tell you at this point if that was statistically significant, but we will certainly go and look at that and get back to the FDA on that particular issue. Thank you.

DR. PETRI: Let me ask Drs. Chambers and Johnson if there are any additional issues that the Agency wished to

bring up.

DR. JOHNSON: No, we don't have any.

DR. PETRI: I think Dr. Silverman had another final comment.

DR. SILVERMAN: I have a question. Would the panel consider any number of patients in systemic JRA prior to an indication? I ask that question really as a pediatric rheumatologist stuck, as pointed by Dr. Simon, with a patients on 1 to 2 mg/kg with terrible systemic disease, and could I one day, if I studied patients appropriately with cyclosporine, is it possible short of a controlled trial to get an indication? Would the panel consider that?

DR. PETRI: A clinical series of well-defined patients, of course, we would.

DR. SILVERMAN: And is there any number that one would come up with to make this practical?

DR. PETRI: Let me ask the pediatric rheumatologists on the panel to pick a number. Dr. Lovell?

DR. LOVELL: I am sorry I wasn't focused. Maybe you can ask one of the others. I was actually thinking about something else.

DR. WHITE: He was just asking how many patients to study, and this is very difficult, you know -- as many as you can get.

DR. SILVERMAN: That could be three, as you know. I am actually trying to be just practical whether it would be worth actually systematically, appropriately collecting the data in a form that would be acceptable to the scientific community.

DR. PETRI: I think what I am suggesting is it need not be a clinical trial. I think a clinical series is acceptable in this kind of situation. Obviously, if there is dissension, I hope the other panel members will say so.

DR. JOHNSON: These are methotrexate failures?

DR. SILVERMAN: Yes, as defined by Dan Lovell.

DR. JOHNSON: High-dose steroid failures?

DR. SILVERMAN: These would be mainly systemics now because I think poly was addressed. These would be high-dose, 1 mg or over.

DR. JOHNSON: How often do they spontaneously remit, that subset?

DR. SILVERMAN: Let me answer that question as we have attempted to design a previous study in systemic JRA, and the answer was the initial attempt was failed because of the controlled trial nature of it, six months of active disease and the ability to get a drug under 1 mg/kg. Those patients would rarely spontaneously remit over the next six-month period.

I think most of the patients will respond in the first six months, and they would not be eligible.

DR. LOVELL: Let me try to salvage something here for polys, poly JRA, and to get back to Dr. Tilley's question, if we had absolutely no data about the effectiveness of cyclosporine in polyarticular JRA, how would we apply the Pediatric Rule.

Now, I think the FDA has said the polyarticular JRA, severe polyarticular JRA has kind of similar course of disease to polyarticular RA in the sense of the severity of articular manifestation or enough similar that we could look at the same drugs.

For cyclosporine, we have the efficacy data that it is efficacious as an add-on to methotrexate. Now, if we could perform a randomized open clinical trial where half of the patients were put on methotrexate and placebo, and half of the patients were put on methotrexate and cyclosporine, but it would be an open clinical trial and run for a sufficient period of time and demonstrate a benefit, statistically significant benefit from the addition of cyclosporine in that polyarticular JRA population, would that be acceptable data to this committee to apply the Pediatric Rule to polyarticular JRA if we had that data? If we could come back to you and say that as in adults, cyclosporine was an

effective add-on drug for methotrexate failures in polyarticular JRA, would this committee be willing to apply the Pediatric Rule and give an indication for polyarticular JRA?

DR. PETRI: In fact, the committee as a whole believe we could invoke the Pediatric Rule with the data that we already have for the polys. It was for the systemics that was voted down.

DR. LOVELL: Is that true? I don't think it was. What was the count?

DR. PETRI: I believe there were three dissenters.

DR. WHITE: Three on the polys.

DR. LOVELL: All right.

DR. JOHNSON: But that kind of evidence, you could argue that it has credence. The trick might be that it is an open study, and if you could refute the assertion that it was a falsely positive study because it was open. We take difference evidence like that all the time, and if methotrexate is just getting consumed in the background therapy, that is not a problem.

DR. PETRI: Kathleen has some closing comments.

MS. REEDY: Tomorrow, the seating arrangement will be different, and for all of your materials for today's meeting, if you would like them shredded, or if you would

like us to take care of them and shred them, bring them to me. If you would like them Fed Ex'd to your office after you leave, please put a note on top of it saying who it belongs to and who we should Fed Ex it to. If you are going to carry them home, please carry them off from the table today.

DR. PETRI: I want to thank everyone for their help today especially the visiting pediatric rheumatologists.

This meeting is adjourned.

[Whereupon, at 4:40 p.m., the proceedings were recessed, to be resumed at 8:00 a.m., Wednesday, February 5, 1997.]